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THE ASSOCIATION OF PITUITARY HYPOFUNCTION WITH CHRONIC DIARRHOEA

A REPORT OF TWO CASES

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Panhypopituitarism is a rare disease and the majority of cases which do occur are either secondary to postpartum haemorrhage or to surgical removal of the gland. It is, however, well-known that features of the condition may occur in persons who are grossly malnourished. A striking point in such cases has been the reversion to normal once the general nutrition has been improved and for this reason such subjects have been labelled as examples of 'functional hypopituitarism'.

The present paper describes two cases of panhypopituitarism in whom chronic diarrhoea with malnutrition antedated the onset of the endocrine disorder. In both subjects the pituitary failure seemed to be severe and irreversible. Because of the variety of such an association, it seems worth while reporting these two cases in detail.

CASE REPORTS

Case 1

A male patient aged 54 years was admitted to the Johannesburg General Hospital in February 1953 with a history of weakness and tiredness over the previous 12 years. He was well until 1941, when he took part in the retreat from Burma. During this period he developed severe diarrhoea, which was diagnosed as being due to both amoebic and bacillary infections of the bowel. He was treated in hospital for several months and, although the diarrhoea cleared up, his general condition remained poor and he was sent back to England. There he was diagnosed as suffering from anaemia but there was no response to a variety of haematinic agents. Over the next years, his condition remained stationary and, although weak, he was able to carry on a sedentary occupation. Apart from the major complaint there were several other changes which the patient noted after the original illness in Burma. He became impotent, was very sensitive to cold, and had to shave only once or twice a week, previously having been of normal hirsuties. These symptoms had persisted up to the time of his admission to hospital.

On examination, he was pale and the skin of the face was finely wrinkled. Facial hair was sparse. Axillary hair was absent and there was very little pubic hair. The pulse rate was 67 per minute and the blood pressure was 120/65 mm. Hg. Nothing abnormal was noted in either the cardiovascular or respiratory systems and nothing abnormal was noted on palpation of the abdomen. The penis was normal in size but the testes were soft and atrophic.

Laboratory data. Packed cell volume 32%, haemoglobin 11·1 g.%, red-cell count 3,760,000 per c.mm. Leucocytes 3,400 per c.mm. (neutrophills 71%, monocytes 6%, lymphocytes 22%, eosinophils 1%, basophils *nil*). Blood electrolytes normal. Modified Ide test negative. X-rays of chest and skull normal. Electrocardiogram normal. Oral sugar tolerance curve (50 g. of glucose)—fasting 69 mg.%, ½ hour 106 mg.%, 1 hour 110 mg.%, 1½ hours 100 mg.%, 2 hours 80 mg.%. Insulin sensitivity test (5 units insulin intravenously)—basal 96 mg.%, ¼ hour 59 mg.%, ½ hour 34 mg.%, 1 hour 41 mg.%, 1½ hours 46 mg.%, 2 hours 51 mg.%. Basal metabolic rate 20%. Robinson-Kepler test positive (factor 8). 17-ketosteroids in 24-hour specimen of urine 2·1 mg. (measured as dehydroisoandrosterone).

Progress. A diagnosis of panhypopituitarism was made on the clinical findings together with the results of the laboratory tests. Replacement therapy was begun with small doses of methyltestosterone, desoxycorticosterone acetate and thyroid extract. Subsequently cortisone was added to the regime. Response to treatment was excellent. There was a marked increase in energy, libido and potency returned, and the blood count gradually reverted to normal. This improvement has been maintained over the ensuing 4½ years.

Case 2

A married European female aged 46 years, with no children, was first admitted to another unit in the Johannesburg General Hospital in January 1956. The major complaints were abdominal pain and intermittent diarrhoea for 10 years. In the 7 months before admission, the diarrhoea had been particularly severe, with the passage of up to 10 motions daily. The stools were sometimes watery and yellow, while on other occasions they were bulky and offensive. The diarrhoea was accompanied by cramplike generalized abdominal pains. Over the 7 months the weight had fallen from 120 lb. to 60 lb. Just before admission to hospital she had noticed some swelling of the ankles.

In the systematic history it was noted that the patient had been pregnant 3 times but on each occasion the infant was stillborn. Postpartum blood loss had not been excessive and she had regular menses for 10 years after the birth of the last child.

She became menopausal at the age of 42.

On physical examination the striking feature was gross emaciation. The tongue was smooth and red. The extremities were cold and there was some peripheral oedema of the lower limbs. The blood pressure was 150/90 mm.Hg. and nothing abnormal was noted in either cardiovascular or respiratory systems. The abdomen was distended with gas and there was a smooth 3-finger hepatomegaly.

Laboratory data. Haemoglobin 13·8 g.%. Leucocytes 9,300 per c.mm. Sedimentation rate (Westergren) 30 mm. in 1 hour. Urine analysis—glucose 4+positive, albumin absent, nothing of significance seen on microscopic examination. Glucose tolerance test (50 g. orally)—fasting 118 mg.%, 1 hour 160 mg.%, 1½ hours 200 mg.%, 2 hours 170 mg.%. serum calcium 4·5 mEq./l., serum inorganic phosphorus 5 mg.%, blood urea 11 mg.%, serum proteins 5·1 g.% (albumin 2·4, globulin 2·7), prothrombin index 100%. Stool examination—macroscopically grey, semi-solid and offensive, microscopically fat globules and muscle fibres present. No pathogenic organisms isolated. Fat balance—21·8g. excreted in 24 hours on diet containing 100 g. of fat. Duodenal intubation—No tryptic activity present. Serum protein-bound iodine 3·3 micrograms %. 17-ketosteroids in 24-hour specimen of urine 2·4 mg. (measured as dehydroisoandrosterone). Follicle-stimulating hormone in 24-hour specimen of urine more than 48 mouse units (normal 12-24 mouse units). Skeletal survey normal. X-rays abdomen—calcification in position corresponding to body and tail of pancreas.

Progress. A diagnosis of severe chronic pancreatitis was made. The steatorrhoea was regarded as being secondary to a deficiency of exocrine secretions and the diabetes as a manifestation of insulin lack. Therapy was started with a high-protein diet, vitamin supplements and a pancreatic extract. In addition, daily insulin (15 units soluble and 15 units protamine zinc) was required in order to stabilize the diabetes. On this treatment the patient gained weight, the diarrhoea subsided to some extent and she felt symptomatically better. She was finally discharged on maintenance therapy 2 months after admission.

Second admission. The patient was readmitted 5 months later, in February 1957, because of an exacerbation of the diarrhoea and for stabilization of the diabetes. There was some doubt whether therapy had been properly followed while she was out of hospital and whether insulin had been taken regularly. Physical findings were similar to those on the previous admission.

Relevant laboratory data: Haemoglobin 11·6 g.%. Urine analysis—glucose 4+ positive. Glucose tolerance test (50 g. orally)—fasting 270 mg.%, ½ hour 312 mg.%, 1 hour 350 mg.%, 2 hours 450 mg.%, 3 hours 472 mg.%, 4 hours 362 mg.%. Serum proteins—total 5·4 g.%, (albumin 1·4, globulin 4·0). 'Liver function' tests—thymol turbidity 5·5 units, zinc sulphate turbidity 16·8 units, alkaline phosphatase 12·2 King-Armstrong units. Total serium lipids 337 mg.%, total serium cholesterol 138 mg.%, serum calcium 5·1 mEq./l. Gastric analysis—histamine-fast achlorhydria.

Progress: Although there had been no major change in the clinical picture, it was felt that some deterioration had occurred. The protein deficit was more marked and the derangement in liver function tests suggested that the malnutrition had caused hepatic degeneration which might be either fibrosis or fatty infiltration. The glucose tolerance test was also more disturbed than on the previous admission. Therapy was begun again and the response was fairly adequate. However, although the diarrhoea became less troublesome, the patient did not gain weight on this admission. Diabetic control was again achieved on a total daily dosage of 30 units of insulin. The patient was discharged again after 1 month in hospital.

Third admission. The patient was first seen by the authors on her third and final admission to hospital in April 1957, only 2 weeks after the previous discharge. While at home she had developed severe diarrhoea and swelling of the legs. Upper abdominal pain, which was cramplike in nature, had also been a feature. During this period she had not taken any insulin.

On physical examination the patient was found to be mentally torpid and very cachectic. The skin was fine and atrophic and a scaly erythematous rash was noted on the trunk and extremities. Spider naevi were present on the forehead and upper chest. The tongue was red and smooth and there was cheilosis at the angles of the mouth. Marked oedema of the legs was present, extending up to the sacrum and vulva. The breasts were atrophic and both axillary and pubic hair were very scanty. No abnormality was noted in the cardiovascular, respiratory and central nervous systems. It was observed that the patient was extremely intolerant to cold and this, coupled with the fine skin and scanty secondary sex hair, raised the possibility that pituitary hypofunction was contributing to the clinical picture.

Laboratory data: Haemoglobin 10·0 g.%, microscopically the red cells showed a tendency to macrocytosis. Urine analysis—*nil* of significance. Glucose tolerance curve (50 g. orally)—fasting 100 mg.%, 1 hour 135 mg.%, 1½ hours 153 mg.%, 2 hours 140 mg.%. Starch tolerance test (50 g. of starch)—fasting 83 mg.%, 1 hour 105 mg.%, 1½ hours 92 mg.%, 2 hours 92 mg.%. Blood urea 19 mg.%, serum proteins 4·5 g.% (albumin 1·1, globulin 3·4). Blood electrolytes—sodium 135 mEq./l., potassium 3·1 mEq./l., calcium 4·1 mEq./l., inorganic phosphorus 2·4 mg.%. Serum cholesterol 120 mg.%, serum protein-bound iodine 2·4 micrograms%. 17-ketosteroids (measured as dehydroisoandrosterone) in 24-hour specimen of urine—0·26 mg. Follicle-stimulating hormone, assay of 24-hour specimen of urine, 6-12 mouse units.

Progress. Despite replacement therapy with intravenous fluids and large doses of oral pancreatic extract, the patient went steadily downhill and died after 2 weeks in hospital. At the time of death the clinical diagnosis was one of chronic pancreatitis with panhypopituitarism in addition.

Autopsy Findings (18 hours after death). The body was emaciated and there was generalized pallor. Oedema was present in both lower extremities and the vulva. The breasts were atrophic. The heart was not enlarged (weight 250 g.); all the valves were competent and healthy: there was slight dilatation of the left ventricle, with thickening of the endocardium; an organized myocardial infarction was present in the interventricular septum; there was a severe degree of atheroma with calcification in the coronary arteries and in the aorta. The smaller arteries showed the presence of arteriosclerosis. The liver was slightly diminished in size (weight 1250 g.); its surface was granular; on section, diffuse cirrhosis and fatty change were noted. The pancreas was grossly diminished in size; it was 4 inches long and ½ inch broad; on section, well marked atrophy and fibrosis were noted; the ducts were dilated and contained white calculi. Central nervous system: the arteries of the circle of Willis showed the presence of atheroma. Endocrine system: the thyroid gland was normal in size; a small adenomatous nodule was present. The pituitary gland was about normal in size; on section an irregular area of dull lustreless yellow colour was seen, occupying about one quarter of the anterior lobe and extending in an irregular manner across the anterior lobe from border to border. The suprarenals showed no macroscopic evidence of abnormality. The parathyroid glands were smaller than normal.

Histopathology. Sections of the pancreas showed advanced fibrosis of the interstitial tissue with a well-marked dilatation of the ducts; a minimal amount of parenchyma was seen, viz. occasional clusters of acini, representing portions of lobules, and in the tail of the gland isolated fragments of islet tissue embedded in dense fibrous tissue; these features are those of chronic cystic pancreatitis. Sections of the liver showed the presence of severe fatty infiltration and diffuse hepatic fibrosis. Section of the heart confirmed the presence of an organized myocardial infarction. Section of the thyroid showed the gland to be in the resting stage. Section of the pituitary showed the presence of necrosis in the anterior lobe; this necrosis was seen in two areas in the posterior portion of the anterior lobe, one on either side of the pars intermedia; the one area of necrosis was about twice the size of the other and together they involved about one quarter of the anterior lobe; they extended from the periphery into the interior of the lobe and were roughly wedge-shaped with their broad bases situated on the periphery of the gland; this distribution is in keeping with avascular necrosis. Sections of the parathyroid glands showed parenchymal atrophy and lipomatosis.

DISCUSSION

The interest of the two cases reported here is the probable association between malnutrition due to chronic diarrhoea and the subsequent hypofunction of the anterior pituitary.

In both the cases this hypofunction seemed to be due to organic rather than functional changes in the gland. This was more clearly demonstrated in case 1, in whom unequivocal signs of irreversible panhypopituitarism developed after a period of prolonged and severe diarrhoea. Despite remission of the diarrhoea the patient's general condition did not improve and he developed weakness, impotence, intolerance to cold, loss of secondary sex hair and a mild refractory anaemia. Biochemical tests, made several years after the onset of the condition, confirmed the presence of pituitary hypofunction and there was a dramatic response to end-organ replacement therapy.

It has been well recognized that pituitary hypofunction can develop in any state of malnutrition. Thus it has been described in starvation, in anorexia nervosa, and secondary to steatorrhoea. However, the striking feature of most reports has been the return to normal once the nutrition has been improved. For example, although Jacobs[1] found a loss of libido, thinning of axillary and public hair and some degree of testicular atrophy in American prisoners of war in a Japanese camp during World War II, these changes were found to be reversible after as long as 40 months of starvation. The same seems to be true in anorexia nervosa. In 1939 Sheldon[2] pointed out that such cases develop a 'functional' type of Simmonds' disease. He felt that a lowering of food intake may lead to a decrease in anterior pituitary function and may thus mimic the findings associated with organic pituitary disease.

There is both clinical and experimental evidence to suggest the validity of such a thesis. For instance, in 1930 Mason and Wolfe[3] found atrophy of the genital system in female rats following on chronic malnutrition and they were able to reverse these changes with pituitary implants. In addition, Weiner (quoted by Hultgren[4]) reported that anoestrus in starving guinea-pigs could be abolished by hypophyseal extracts.

Of special interest are those cases of hypopituitarism which have been reported in association with diarrhoea. In 1939 Bauer[5] drew attention to the endocrine changes in sprue and suggested that these were due to the concomitant nutritional deficiency. More recently (1952) Hubble[6] reported a case of adult coeliac disease presenting features quite similar to those in case 1. The patient was a female, aged 38 years, who had suffered from repeated attacks of diarrhoea since childhood. Menstruation had been irregular before it ceased one year prior to examination. The physical findings included pallor and scanty pubic axillary hair. The daily excretion of 17-ketosteroids had dropped from 5 mg. 1 year previously to 2·5 mg., while gonadotrophins and oestrogens were absent in the urine. The condition seems to have been functional rather than organic since menstruation subsequently returned when the patient was kept on a gluten-free diet, and urinary oestrogens and gonadotrophins are now normal. However, it still remains possible that chronic diarrhoea with malnutrition may, in isolated instances, lead to irreversible pituitary damage. A probable example of such a case is one reported by Salamon and Lascano[7] in 1942. They found evidence of Simmonds' disease in a male patient who had suffered from steatorrhoea for 5 years. At autopsy there was a diffuse sclerosis of the gland and 2 foci of ischaemic necrosis. In addition, atrophy of the thyroid and testes was present.

From these findings it appears as if the dividing line between functional and organic pituitary damage is not always a clear one. Perloff *et al.*,[8] in 1954, after reviewing the literature came to the conclusion that functional hypopituitarism differs from the organic variety in only two respects. Firstly, the syndrome can be abolished by re-feeding and, secondly, recognizable changes in the structure of the anterior lobe of the pituitary are either absent or slight. Actual histological changes in the pituitary following on malnutrition have, in fact, been reported by a number of workers. In 1948 D'Angelo *et al.*[9] were able to demonstrate an arrest of cellular mitosis, vacuolization of cytoplasm, loss of staining reactions, and a reduction in the number of cells in starving rats. In addition, Gillman and Gillman[10] have reported the presence of cellular changes and small destructive foci in the anterior pituitary lobes of subjects dying from starvation.

From these various findings reported by other workers, it seems reasonable to suppose that case 1 in the present paper represents an example of a rare but real entity—irreversible pituitary damage initiated by a period of severe diarrhoea with associated malnutrition. The interpretation of case 2, however, is more difficult. This patient had suffered from chronic pancreatitis with diabetes, steatorrhoea and protein deficit for several years. Clinically she showed the features of pituitary insufficiency as evidenced by extreme intolerance to cold, hoarseness, loss of secondary sex hair and anaemia. In addition, the diabetes showed a striking amelioration in the last few weeks of life. Glycosuria disappeared and the sugar-tolerance curve returned towards normal. At this stage she became so sensitive to the effects of insulin that it was discontinued and serial laboratory studies demonstrated an appreciable fall in serum protein-bound iodine and in the urinary excretion of follicle-stimulating hormone and 17-ketosteroids. At autopsy 30% of the anterior pituitary was found to be necrosed.

It is possible that the pituitary necrosis present in case 2 was secondary to the chronic malnutrition. However, it is well recognized that it may have been related to the diabetes from which she suffered. This association has been recorded by a number of investigations,[11-14] In a review in 1956 of 7,326 autopsies in adults, Brennan *et al.*,[15] found that some degree of pituitary necrosis was present in 2·0% of diabetes subjects as opposed to an incidence of 0·2% in non-diabetics. On the basis of such studies, diabetes mellitus has been estimated as a cause of between 1% (Escamilla and Lisser, 1942)[13] and 8% (Plaut, 1952)[16] of cases of pituitary failure.

In case 2 it is therefore impossible to dogmatize on the relative roles played by malnutrition and diabetes in the genesis of the pituitary hypofunction. It seems probable that both were involved. It is also not easy to relate the amount of pituitary necrosis revealed at autopsy to the undoubted clinical evidence of severe pituitary hypofunction. In 1949 Sheehan and Summers [14] showed that 75% or more of the pituitary must be destroyed before clinical manifestations of hypofunction appear. However, these findings relate to cases of postpartum haemorrhage in whom the remainder of the gland was healthy. In case 2 this was almost certainly not so, for the function of the gland had been depressed by chronic malnutrition. On such a background the occurrence of limited necrosis was probably sufficient to cause the changes in endocrine function which were evident on the patient's last admission.

Of these changes the alteration in glucose tolerance was perhaps the most striking. The endocrine antagonism between the pituitary and pancreas is well established. For

example, it has been found that the diabetes produced in dogs by extirpation of the pancreas can be ameliorated by the removal of the anterior pituitary. Such dogs are hypersensitive to insulin and brief fasting produces severe hypoglycaemia.[17-19] Young,[20] also found that diabetes could be produced in dogs given large amounts of pituitary extract over long periods.

In effect, case 2 represented an example of the Houssay phenomenon in man. Although examples of such cases are rare, Harvey and de Klerk[21] in an excellent review of the subject in 1955 analysed 11 cases reported in the literature and added 3 of their own. It has been possible to find reference to a further 7 cases[22-27, 15] which, with the present example make a total of 22 reported cases. The condition usually involves individuals who have had diabetes mellitus for a considerable time and is usually caused by infarction of the anterior lobe of the pituitary gland. One of the first manifestations is hypoglycaemia with extreme sensitivity to administered insulin. Within a month or two signs of thyroid, adrenal and gonadal insufficiency begin to appear. The diabetes is ameliorated rather than cured and the glucose-tolerance curve usually remains diabetic in type.

SUMMARY

Two cases are reported in which the presence of severe malnutrition, associated with chronic diarrhoea was followed by evidence of permanent pituitary damage. This is best illustrated in case 1, where replacement therapy produced an excellent and lasting response. Case 2 was found to have pituitary necrosis at autopsy. Aetiological factors may well have been chronic diarrhoea and malnutrition, although the presence of diabetes mellitus might also have played a role.

Attention is drawn to the scanty reference in the literature to organic pituitary damage occurring in cases of malnutrition associated with chronic diarrhoea.

The relation between diabetes and pituitary necrosis is briefly reviewed.

The possible endocrine link-up between organic and functional hypopituitarism as seen in malnutrition, anorexia nervosa, starvation, and chronic diarrhoea is discussed.

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REFERENCES

1. Jacobs, E. C. (1948): J. Clin. Endocr. **8**, 227.
2. Sheldon, J. H. (1939): Proc. Roy. Soc. Med., **32**, 738.
3. Mason, K. and Wolfe, J. (1930): Anat. Rec., **45**, 232.
4. Hultgren, H. N. (1951): Stanford Med. Bull., **9**, 175.
5. Bauer, J. (1939): J. Trop. Med., **42**, 245.
6. Hubble, D. (1952): Lancet, **1**, 1123.
7. Salomon, H. and Lascano, J. C. (1942): Sem. méd., **49**, 746.
8. Perloff, W. H., Lasche, E. M., Nodine, J. H., Scheeberg, N. G. and Vieillard, C. B. (1954): J. Amer. Med. Assoc., **155**, 1307.
9. D'Angelo, S. A., Gordon, A. S. and Charipper, H. A. (1948): Endocrinology, **42**, 399.
10. Gillman, J. and Gillman, T. (1951): *Perspectives in Human Malnutrition* New York: Grune and Stratton, Inc.
11. Kraus, E. J. (1920): Virchows Arch. Path. Anat., **228**, 68.
12. Kiyono, H. (1926): *Ibid.*, **262**, 149.
13. Escamilla, R. F. and Lisser, H. (1942): J. Clin. Endocr., **2**, 65.
14. Sheehan, H. L. and Summers, V. K. (1949): Quart. J. Med. n.s., **18**, 319.
15. Brennan, C. F., Malone, R. G. S. and Weaver, J. A. (1956): Lancet, **2**, 12.
16. Plaut, A. (1952): Amer. J. Path., **28**, 883.
17. Houssay, B. A. and Biasotti, A. (1930): Rev. Soc. argent. Biol., **6**, 251.
18. *Idem* (1931): Arch. ges. Physiol., **227**, 664.
19. Houssay, B. A. (1936): New Engl. J. Med., **214**, 971.
20. Young, F. G. (1937): Lancet, **2**, 372.
21. Harvey, J. C. and de Klerk, J. (1955): Amer. J. Med., **19**, 327.
22. Alexander, R. I. (1953): Brit. Med. J., **1**, 1416.
23. Martin, M. M. and Pond, M. H. (1954): J. Clin. Endocr., **14**, 1046.
24. Levin, M. E. (1954): Ann. Intern. Med., **40**, 1230.
25. Brenner, J. H. (1955): Diabetes, **4**, 223.
26. Brouwer, K. and Schopman, W. (1955): Ned. T. Geneesk., **99**, 1506.
27. Calvert, R. J. and Caplin, G. (1957): Brit. Med. J., **1**, 71.

BOOKS RECEIVED : BOEKE ONTVANG

Die Geburtshilflichen Operationen. Ihre Ausführung und Anwendung. Ein Lehrbuch für Studenten und Gebrauchsbuch für Ärzte. Von Prof. Dr. H. Martius. 8., Verkürzte und verbesserte Auflage. XVI + 281 Seiten. 253 Abbildungen. DM 29.60. Stuttgart: Georg Thieme Verlag. 1958.

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Lehrbuch der röntgenologischen Differentialdiagnostik. Band I: Erkrankungen der Brustorgane. 4., Verbesserte und erweiterte Auflage. Von Prof. Dr. W. Teschendorf, unter Mitarbeit von Priv.-Doz. Dr. P. Thurn. XII + 1,183 Seiten. 1,138 Abbildungen. DM 210.00. Stuttgart: Georg Thieme Verlag. 1958.

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VAN DIE REDAKSIE

DIE MEGANISMES VERANTWOORDELIK VIR HASHIMOTO SE SIEKTE, EN VERWANTE AANGELEENTHEDE

Die ontdekking van verhoogde gammaglobuliene en abnormale serum-proteïen-uitvlokkingtoetse by Hashimoto se siekte,* hul geleidelike terugkeer na normaal, ná die verwydering van die kropgeswel,[1-3] en die infiltrasie van die tiroïed deur selle wat ons weet teenliggaampies vervaardig, het Roitt en sy medewerkers laat postuleer dat hierdie veranderings veroorsaak word deur 'n immuniseringproses wat teen die skildklier gerig is. Hulle het toe aangetoon dat die bloedwei van pasiënte met hierdie soort kropgeswel presipiterende teenliggaampies teen menslike tiroglobulien bevat.

Die teenliggaampies is blykbaar spesifiek teen tiroglobulien gerig, want negatiewe uitslae is met ekstrakte van ander menslike weefsels behaal. Die presipitiene was aantoonbaar wanneer ongesuiwerde skildklierekstrakte uit normale en vergiftigende kliere gebruik was en dié het 'n beperkte spesie-spesifisiteit getoon. Ná die fraksioneer van die pasiënte se serum deur sone-elektroforese op sellulose-kolomme en deur immuun-elektroforese, is dit bevind dat dit die gammaglobulien was wat die presipiterende teenligaampies bevat.

Roitt en Doniach[5] het die bloedwei van 107 lyers aan Hashimoto se siekte ondersoek. Sewentig van hulle was glad nie behandel nie, of slegs met tiroïedhormoon behandel, en by 52 van hulle was die presipitientoetse positief. Op een na het die 18 negatiewes positief gereageer toe hulle deur komplement-fiksering getoets is—ekstrakte van 'n tirotoksiese klier is as antigeen gebruik. Die serum van die pasiënt wat negatief op beide toetse gereageer het, is vervolgens deur 'n meer sensitiewe presipitienmetode bestudeer, en daar is bewys dat dit wel 'n sekere hoeveelheid teenstof bevat het, hoewel minder as die ander. Uit die 37 ná-operatiewe Hashimoto-serums, het slegs 14 positiewe presipitientoetse gelewer, en dit is bevind dat die voorkomssyfer van negatiewe uitslae toeneem namate groter gedeeltes van die skildklierweefsel verwyder word en namate 'n langer tydperk na die operasie verstryk. Roitt het voorts die serums van 238 pasiënte met ander skildkliersiektes deur middel van die presipitientoets ondersoek. Nie een van die pasiënte met skildkliervergiftiging of nie-toksiese nodulêre krop het enige presipitien in hul serums getoon nie. Verbasend genoeg het 6 uit 33 pasiënte met primêre miksedeem, en

* Hashimoto se siekte is in verlede week se uitgawe van hierdie *Tydskrif* (bl. 395) deur die redaksie bespreek.

EDITORIAL

MECHANISMS RESPONSIBLE FOR HASHIMOTO'S DISEASE, AND RELATED CONSIDERATIONS

The finding of raised gamma globulins and abnormal serum-protein flocculation tests in Hashimoto's disease,* their gradual return to normal after the removal of the goitre,[1-3] and the infiltration of the thyroid gland by cells known to produce antibody, led Roitt and his co-workers to postulate that these changes were caused by an immune process directed against the thyroid. They then demonstrated that the sera of patients with this type of goitre contained precipitating antibodies against human thyroglobulin.

The antibody was apparently specifically directed against thyroglobulin, since negative results were obtained against extracts of other human tissues. The precipitins were demonstrable when crude thyroid extracts from normal or thyrotoxic glands were used, and these showed a narrow species specificity. After fractionation of patients' serum by zone electrophoresis on cellulose columns and by immuno-electrophoresis, it was found that the precipitating antibody was contained in the gamma globulin.

Roitt and Doniach[5] examined sera from 107 patients with Hashimoto's disease. Seventy of these were untreated or treated with thyroid hormone only and 52 of them gave positive precipitin tests. All but one of the 18 negative ones gave positive results when tested by complement fixation, extracts of thyrotoxic gland being used as antigen. The one serum which was negative to both tests was then further studied by a more sensitive precipitin method and shown to contain some antibody, though less than the others. Of 37 post-operative Hashimoto sera, only 14 gave positive precipitin tests, and the incidence of negative results was found to increase with the amount of thyroid tissue removed and with the length of time elapsed since the operation. Roitt proceded to examine the sera of 238 patients with other thyroid diseases by the precipitin test. No patients with thyrotoxicosis or non-toxic nodular goitre had any precipitins in their sera. Surprisingly, 6 patients with primary myxoedema out of 33, and 4 with subacute thyroiditis, also gave quite strong precipitin tests.

* Hashimoto's disease was the subject of an editorial in last week's issue of this *Journal* (page 395).

4 met subakute skildklierontsteking ook taamlike sterk presipitientoetse gelewer.

Die aantoon by die chroniese skildklierontsteking van Hashimoto van teenliggaampies in omloop, wat teen die pasiënt se eie skildklier werk, en die bevestigde selvergiftigende uitwerking van eksperimenteel verkrygde outo-immunisering, het daarop gedui dat die siekte moontlik deur 'n self-voortsettende vernietigingsproses ontstaan wat afhang van 'n immuunreaksie teen tiroglobulien of die een of ander proteïen in die skildklier. Roitt wys daarop dat aangesien tiroglobulien gewoonlik tot die follikels beperk is en nie vry sirkuleer nie, indiwidue nie gewoonweg 'n immunologiese verdraagsaamheid daartoe sal ontwikkel nie.

In hierdie verband het Witebsky en Rose[6,7] daarin geslaag om verskeie dieresoorte teen ekstrakte van soortgelyke skildkliere te immuniseer en het letsels in die skildkliere van sodanig behandelde diere waargeneem wat in baie opsigte ooreenstem met chroniese skildklierontsteking by die mens. Ons kan dus aanneem dat, by die mens, 'n uitstorting van tiroglobulien uit die follikel 'n reaksie van outo-immunisering kan uitlok en die indring van limfatiese selle tot die klier kan stimuleer, met gevolglike plaaslike vorming van teenliggaampies; die aangrensende follikels word sodoende beskadig en stel dan nog meer kolloïed vry. Met verloop van tyd kan die aantasting van die skildklier versprei, en afgeleë dele van die retikulo-endoteelstelsel kan by die produseer van teenliggaampies betrokke raak. Die klassieke geval van Hashimoto se siekte is 'n gevorderde en uiterste voorbeeld van hierdie proses.

Die ontdekking van presipitiene in die serum van pasiënte met primêre miksedeem sonder kropgewas, suggereer dat sommige gevalle van miksedeem 'n ander kliniese gevolg van dieselfde immunologiese proses kan wees. By die soort miksedeem wat ons by die Hashimoto-siekte teëkom, ontdek ons 'n fibrotiese klier met limfsel-infiltrasie. Histologies is hierdie twee kondisies merkwaardig eners—die verskil is dat daar by die een 'n kropgewas, en by die ander 'n abnormaal klein klier gevind word. Roitt meld dat die ontwikkeling van 'n kropgewas as gevolg van tirofede self-immunisering moontlik op die vermoë van die klier om op TSH te reageer, berus.

Trotter,[8] wat die komplement-fikseringtoetse op hierdie probleem toegepas het, het teenliggaampies ook by 'n aantal pasiënte met skildkliervergiftiging aangetref. Hy vestig die aandag daarop dat kolle van limfweefselagtige selverandering in sommige kropgeswelle aangetref word en stel dus voor dat daar moontlik 'n verband bestaan tussen hierdie verandering en die aanwesigheid van komplement-fikserende teenliggaampies. Die navorsing wat tans gedoen word, kan dus die geleentheid bied om iets te leer oor die meganismes betrokke by Hashimoto se skildklierontsteking sowel as by primêre skildkliervergiftiging.

White[9] het die setel van die betrokke antigeen deur middel van die gloeigas-metode vir teenliggaampies ondersoek. Hy het bevind dat die antigeen, wat die Hashimoto-teenliggaampie lokaliseer, teenwoordig is binne die follikels, in die selle van die follikel-epiteel, en ook buitekant die follikels, in en rondom die infiltrerende limfselle.

Dit blyk dus dat die antigeen vryelik uit die follikels vloei, en dit is dus begryplik dat teenliggaampies gevolglik gevorm kan word. White het verder die aangrensende limfknope ondersoek en ontdek dat die periferale limfholtes

The demonstration of circulating antibodies against the patient's own thyroid gland in the chronic thyroiditis of Hashimoto, and the known cytotoxic effects of experimentally induced auto-immunization, suggested that the disease might arise by a self-perpetuating destructive process depending upon an immune response to thyroglobulin or some other protein in the thyroid gland. Roitt points out that since thyroglobulin is normally confined in the follicles and does not circulate freely, individuals will not normally acquire an immunological tolerance to it.

In this connection Witebsky and Rose[6,7] succeeded in immunizing several animal species against extracts of homologous thyroid glands and observed lesions in the thyroids of animals so treated which have many features in common with human chronic thyroiditis. Thus we may suppose that in the human subject a release of thyroglobulin from the follicle might elicit an auto-immune response and stimulate invasion of the gland by lymphoid cells with local antibody production, so causing damage to adjacent follicles with further release of colloid. In time the thyroid gland might become diffusely involved, and distant parts of the reticulo-endothelial system might be implicated in the production of antibodies. Classical Hashimoto's disease represents a late and extreme example of this process.

The finding of precipitins in the sera of patients with primary myxoedema without goitre suggests that some cases of myxoedema may represent another clinical result of the same immunological process. In myxoedema as in Hashimoto's disease we find a fibrotic gland with lymphoid infiltration. Histologically these two conditions are remarkably similar—except that in one there is a goitre and in the other a smaller than normal gland. Roitt remarks that the development of a goitre as a result of thyroid auto-immunity may depend on the ability of the gland to respond to TSH.

Trotter,[8] who applied the complement-fixation tests to the problem, found antibodies also in a number of patients with thyrotoxicosis. He points out that patchy lymphadenoid change is seen in some toxic goitres and hence suggests that there may be a correlation between this change and the presence of complement-fixing antibodies. Thus the present work may provide an opportunity for learning something of the mechanisms involved not only in Hashimoto's thyroiditis, but also in primary myxoedema and in primary thyrotoxicosis.

White[9] has investigated the localization of the antigen concerned by fluorescent antibody technique. He found that the antigen which localized the Hashimoto antibody was present within the follicles, in the cells of the follicular epithelium, and also outside the follicles, in and among the infiltrating lymphoid cells. Thus the antigen appears freely to pass out of the follicles, and it is easy to see that antibody formation might then result. White further examined the adjacent lymph nodes and found that the peripheral lymph sinuses of the nodes were crowded with large reticulo-

van die knope propvol groot retikulo-endoteelselle was wat sitoplasmiese ronde korreltjies van teenliggaampies bevat. Die antigeen bereik dus vermoedelik die limfknope langs die limfvate en vorm presipitiene met die teenliggaampie van die limf, wat dan opgeneem word deur die sinus-voeringfagosiete.

Die meganismes verantwoordelik vir die ontstaan van 'n obskure siekte is dus, binne die bestek van 'n baie kort tydjie, grotendeels toegelig en die bevindings klop op alle punte. Bowendien word ons gedwing tot die besef dat die siekte betreklik dikwels voorkom, en dat dit nou met heelwat sekerheid gediagnoseer en wetenskaplik behandel kan word. Die betrokke meganisme—een van outo-immunisering teen 'n antigeen spesifiek op 'n besondere orgaan gerig—hoewel maar pas ontdek, kan moontlik buite die enge bestek van Hashimoto se siekte van toepassing wees.

1. Luxton, R. W. en Cooke, R. T. (1956): Lancet, **2**, 105.
2. Skillern, P. G., Crile, G., McCullach, E. P., Hazard, J. B., Lewis, L. A. en Brown, H. (1956): J. Clin. Endocr., **16**, 35.
3. Doniach, D. en Hudson, R. V. (1957): Brit. Med. J., **1**, 672.
4. Roitt, I. M., Doniach, D., Campbell, P. N. en Hudson, R. V. (1956): Lancet, **2**, 820.
5. Roitt, I. M. en Doniach, D. (1957): Proc. Roy. Soc. Med., **50**, 959.
6. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R. en Egan, R. W. (1957): J. Amer. Med. Assoc., **164**, 1439.
7. Rose, N. R. en Witebsky, E. (1956): J. Immunol., **76**, 417.
8. Trotter, W. R., Belyavin, G. en Waddams, A. (1957): Proc. Roy. Soc. Med., **50**, 961.
9. White, R. G. (1957): *Ibid.*, **50**, 953.

endothelial cells containing cytoplasmic spherical granules of antibody. The antigen thus presumably reaches the lymph nodes *via* the lymphatics and forms precipitins with the antibody of the lymph, which are then taken up by the sinus-lining phagocytes.

In a very short time, then, the mechanisms responsible for the production of an obscure disease have been largely elucidated and the findings fit together at all points. Furthermore we have been made to realize that the condition is relatively common, and may now be diagnosed with considerable certainty and treated on a scientific basis. The mechanism responsible—one of auto-immunization against an organ-specific antigen—, though newly recognized, is one which may have application beyond the narrow field of Hashimoto's disease.

1. Luxton, R. W. and Cooke, R. T. (1956): Lancet, **2**, 105.
2. Skillern, P. G., Crile, G., McCullach, E. P., Hazard, J. B., Lewis, L. A. and Brown, H. (1956): J. Clin. Endocr., **16**, 35.
3. Doniach, D. and Hudson, R. V. (1957): Brit. Med. J., **1**, 672.
4. Roitt, I. M., Doniach, D., Campbell, P. N. and Hudson, R. V. (1956): Lancet, **2**, 820.
5. Roitt, I. M. and Doniach, D. (1957): Proc. Roy. Soc. Med., **50**, 959.
6. Witebsky, E., Rose, N. R., Terplan, K., Paine, J. R. and Egan, R. W. (1957): J. Amer. Med. Assoc., **164**, 1439.
7. Rose, N. R. and Witebsky, E. (1956): J. Immunol., **76**, 417.
8. Trotter, W. R., Belyavin, G. and Waddams, A. (1957): Proc. Roy. Soc. Med. **50**, 961.
9. White, R. G. (1957): *Ibid.*, **50**, 953.

FLATULENT DYSPEPSIA*

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'Flatulent dyspepsia' is one of the commonest ailments of man, ranking with 'rheumatism' and 'headache' in its ubiquity; and, like them, it is not a disease but a manifestation of an underlying condition which may be trivial, serious or fatal. It does, however, form a well-knit symptom-complex which may be defined as upper abdominal discomfort related, though sometimes vaguely, to meals and associated with heartburn, eructations and acid regurgitation. In severe cases angina-like chest pains, high backache and dysphagia may also be experienced. The causes of this syndrome are many and may be listed as:

1. Normal or Physiological Conditions
   (*a*) Pregnancy
   (*b*) Obesity
   (*c*) Gastric distension—gluttony, aerophagy, etc.
2. Disease States
   (*a*) Hiatus hernia
   (*b*) Peptic ulceration of stomach and duodenum
   (*c*) Cholecystitis and cholelithiasis
   (*d*) Appendicitis
   (*e*) Abdominal herniae
   (*f*) Abdominal tumours—fibroids, pancreatic cysts, etc.

Though flatulent dyspepsia may be common to all these varying conditions, it is often possible to distinguish the cause clinically because of the presence of additional symptoms more or less specific to the underlying condition.

* A paper presented at the South African Medical Congress, Durban, September 1957.

Flatulent dyspepsia is a non-specific syndrome as far as disease states are concerned, yet it is highly specific to its basic underlying cause. Acid eructations, heartburn and flatulence, when present together, denote only one thing—gastro-oesophageal regurgitation. It is interesting to determine why affections of so many different organs should cause gastro-oesophageal regurgitation and for this it is necessary, in the first place, to understand the mechanism of reflux of stomach contents into the oesophagus.

The Mechanism of Prevention of Regurgitation

Because the abdominal pressure is positive and the thoracic pressure negative, the pleuroperitoneal pressure gradient constantly tends to displace stomach contents into the oesophagus. In spite of this, continuous regurgitation is in some way prevented. It is commonly agreed that this is mainly accomplished by the oblique entry of the oesophagus into the stomach, which acts as a flap-valve when the stomach distends. Several experiments on young male cadavers were designed to confirm this belief (Marchand, 1955):

The pylorus was cannulated and the stomach distended with water from a reservoir which was raised alongside a measured rule until the water was seen to escape from the oesophagus.

The experimental findings illustrated in Fig. 1 clearly confirm the importance of the mechanical arrangement of the fundus. When the fundus is excluded from the rest of the stomach (Fig. 1B), the resistance offered by the cardia to regurgitation is diminished threefold.

When the left leaf of the diaphragm is removed to allow the

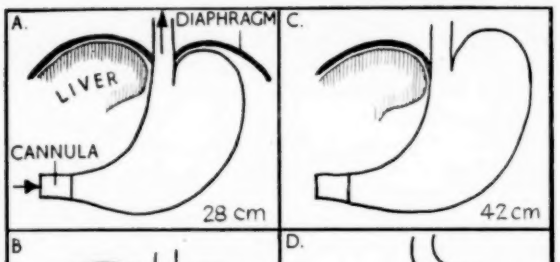

Fig. 1. Illustration of experiment designed to show the importance of the normal acute angle of entry of the oesophagus into the stomach in preventing reflux of stomach contents (see text). The pressures, in cm. of water, denote the force at which reflux occurs under the experimental condition illustrated. The dotted line in B illustrates position of the clamp used to obliterate the fundus of the stomach. In D the liver and diaphragm were completely removed.

fundus to bulge upwards without hindrance, the pressure necessary to induce regurgitation is increased by half again (Fig. 1C).

The liver tunnel, the crura, and the pressure of surrounding organs, are important in maintaining the relative positions of the stomach and oesophagus and the efficiency of the cardio-oesophageal angle (Fig. 1D).

During barium examination of a patient with hiatal hernia, a condition in which the gastro-oesophageal angulation is abolished, it is often possible to demonstrate a weak barrier to regurgitation from the intrathoracic stomach. Johnstone (1946) believes that this is evidence for an intrinsic sphincter at the cardio-oesophageal junction. This view is supported by the following experiments.

Twenty normal young adults were subjected to controlled abdominal compression in the head-down position by means of a balloon incorporated in a corset. (Marchand, 1952). The stomach was filled by drinking watery barium and the balloon was then gradually inflated until regurgitation was seen or until a pressure of 150 cm. of water was reached. The following general conclusions were made:

1. The higher the pressure at which reflux was produced, the more forcible was regurgitation. For instance, pressures of 60 cm. of water seldom caused barium to regurgitate into the cervical oesophagus, whilst pressures of 150 cm. of water usually did so and frequently forced the barium into the mouth.
2. Regurgitation is facilitated by the act of swallowing. If a constant abdominal pressure is maintained whilst the stomach is distended with barium then, at the very instant of swallowing, the barium already in the stomach regurgitates powerfully.
3. Regurgitation is sometimes seen when an oesophageal peristaltic wave reaches the cardia. This observation was reported by Johnstone (1951) and is to be distinguished from the reflux which occurs at the inception of a swallowing effort.

These observations illustrate two fundamental points:

1. The force which causes regurgitation is the intragastric pressure.

2. The acute oesophago-gastric angle is reinforced by some active intrinsic mechanism which can be inhibited by swallowing; in other words an intrinsic sphincter is present.

The acute angle of oesophageal entry into the stomach and the weak inherent sphincter are the immediate factors which prevent free gastro-oesophageal regurgitation. The normal angle of entry, however, is maintained intact by surrounding structures such as the liver and more particularly the diaphragm. The prime need is that the cardia remains at diaphragm level and this depends largely upon the preservation of the optimal size and shape of the oesophageal hiatus. The normal hiatus is elliptical in shape. This shape is maintained by the direction of the crural muscle fibres, the anterior decussation of these fibres and the ligaments and membranes of the diaphragm (Fig. 2). The most important of these

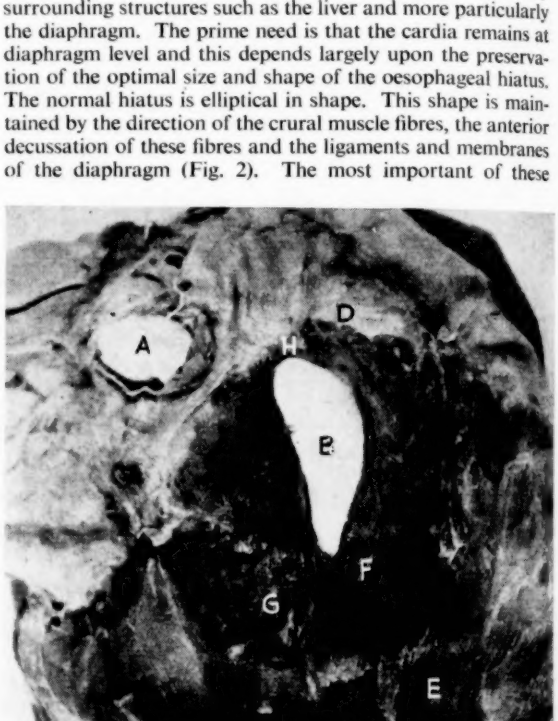

Fig. 2. Dissection of hiatal structures viewed from below. Note that the elliptical shape of the hiatus arises naturally from the origin and insertion of the hiatal limbs, which in this case are derived entirely from the right crus. A=Inferior vena cava. B=Oesophageal hiatus. C=Aorta. D=Transverse membrane of central tendon of diaphragm. E=Left crus. F=Left hiatal limb of right crus. G=Right hiatal limb of right crus. H=Anterior decussating muscle fibres.

latter are the phreno-oesophageal ligament and the transverse membrane of the diaphragm. So long as this shape is maintained and the size remains sufficient only to transmit the oesophagus, the hiatal limbs will provide direct support to the gastro-oesophageal ligament (Marchand, 1957). Should diaphragmatic support be lost by widening of the hiatus, the phreno-oesophageal ligament must bear the full brunt of the abdominal pressure. The cardia will be displaced upwards and the acute angle of entry of the oesophagus into the stomach will be altered.

THE MECHANISM OF REGURGITATION

Theoretically, regurgitation could be due to one of two basic causes:

1. Increase of the intragastric pressure above levels normally withstood by the resisting mechanism.
2. Weakening of the anatomical sphincter mechanism.

1. *Increase of Intragastric Pressure*

Regurgitation can be induced simply by elevating the intragastric pressure. This may be due to active or passive causes.

Passive Causes. Cannon (1911) has shown that the stomach, like the bladder, accommodates for its increasing contents by reflex relaxation of its muscular walls, so that excessive pressure rise is prevented. However, considerable and sharp elevation in tension is caused by postural changes such as stooping, bending forwards, or lying supine. Fig. 3 illustrates graphically the rise in pressure within the stomach of a subject who adopts the 'head-down' position. This is an entirely physical phenomenon caused by the direction of the thrust of the abdominal contents affected by gravity.

Gastric distension also affects the intragastric pressure, and this can be proved by simple experiment. A subject is given graduated amounts of watery barium to swallow against a constant abdominal compression force of 120 cm. of water (by means of the balloon technique described above) and the effects are then viewed by radioscopy. In a series of 10 young adults, no one regurgitated after 500 ml. had been swallowed, 3 regurgitated after 1000 ml. had been taken and 5 others after 1500 ml. The effect of gastric distension has been recorded manometrically and Fig. 4 shows the immediate rise in gastric pressure caused by swallowing an effervescent powder.

Intraperitoneal pressures are passively transmitted to the stomach and when the peritoneal capacity is decreased, as in pregnancy or adiposity, slight postural changes will cause an inordinate rise in the intragastric tension. The effects of diaphragmatic contraction also cause a considerable pressure variation within the stomach and with deep inspiration the pressure gradient between stomach and oesophagus may be very considerable (Fig. 5). With straining, both pleural and peritoneal pressures rise so that the gradient at first remains constant. Only on very forceful exertion does the pressure gradient across the diaphragm rise sharply. (Marchand 1955 and 1957).

Active Causes. Gastric contractions can also cause a sharp increase in the intragastric pressure particularly if the stomach is distended. Normally it is the empty stomach which is the most active, whereas the full stomach is at rest (Alvarez, 1948). When gastric contractions are associated with pyloric closure the intragastric pressure may rise violently and cause regurgitation. This is what happens during vomiting.

2. *Weakening of Anatomical Sphincter Mechanism*

Disruption of the normal oesophago-gastric angle occurs classically in sliding hiatus hernia. In this condition the cardia is displaced upwards into the chest and the normal anatomical angle is abolished. The tonic contraction of the terminal oesophagus still provides a weak defence, and an increase in gastric tension following postural change, deep inspiration, etc., is usually necessary to cause regurgitation. The tonic closure of the terminal oesophagus seems just capable of withstanding the normal pleuroperitoneal pressure gradient.

DISCUSSION

The results of the experiments and observations here described are supported by clinical experience. It is almost

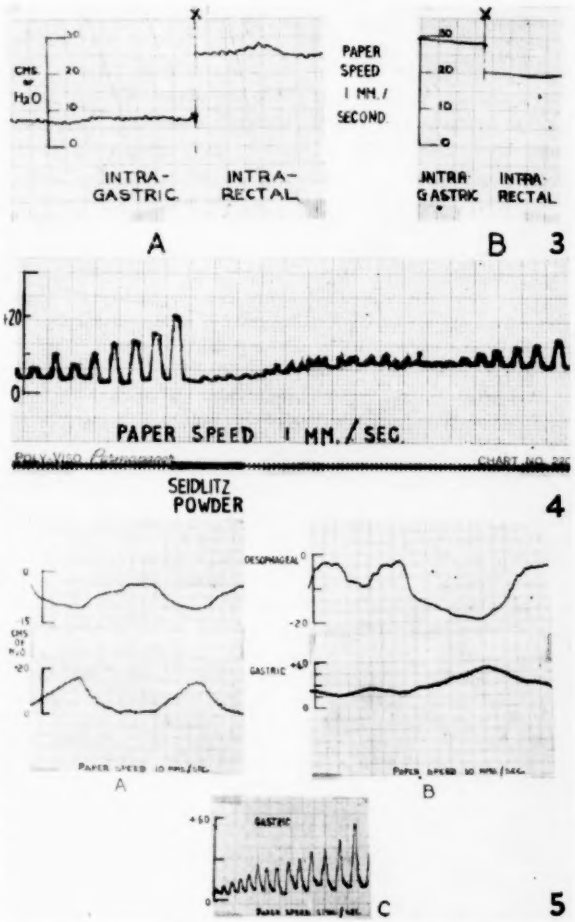

Fig. 3. Immediately consecutive intra-gastric and intra-rectal pressure tracings. A. With the subject erect, the gastric pressure is 18 cm. of water less than in the rectum. B. With the subject inclined head-downwards at an angle of 45° from the horizontal, the intra-gastric pressure is 8 cm. of water higher than the rectal. Reproduced from *Thorax* (1957): **12**, 189.

Fig. 4. Gastric pressure tracing illustrating the effect of distention with gas. The second Seidlitz powder was swallowed whilst the continuous line by the time-marker was being written. There is an immediate rise in the basal gastric pressure. The subject progressively increased the depth of inspiration before and after the powder was taken. Reproduced from *Thorax* (1957): **12**, 189.

Fig. 5. Simultaneous intra-gastric and intra-oesophageal pressure. A. Normal respiration. B. Deep respiration. C. Only gastric pressure recorded, with progressively deepening inspiration. With quiet respiration a pressure gradient of 30 cm. of water exists across the diaphragm. This rises to 60 cm. of water on deep breathing. Reproduced from *Thorax* (1957): **12**, 189.

invariable to find, when investigating a case of flatulent dyspepsia, either that there is some cause for an enhanced regurgitating force or some cause for a weakened defence. Pregnant women constantly complain, and well they might for, in addition to a rapidly growing abdominal tumour which raises the weight and pressure of the abdominal contents, they suffer the effects of softening and laxity of the collagen fibres in their muscles and membranes. As a consequence, the support which the hiatus affords the cardia is weakened and hiatus herniation is not uncommon.

The second large group of sufferers are previously vigorous men who abandon active sport in their thirties and then gain weight. In the presence of a still strong abdominal musculature the accumulation of abdominal fat causes a marked rise of the basal abdominal pressure and the development of flatulent dyspepsia. Not infrequently the inexorable pressure disrupts the hiatus, resulting in hiatus herniation, though they may be saved from this, and cured of their dyspepsia, by losing abdominal muscle tone and increasing their abdominal capacity so that a sagging or rotund paunch develops.

Our wasp-waisted grandmothers paid the price of fashion in flatulent dyspepsia; their repressive corsets left little room for a well-filled stomach. All of us have suffered, at least occasionally, either because we have filled our stomachs to drum-like tension in an act of gluttony, or because we have eaten a particular food which causes our pylorus to close in protest. Similarly duodenal ulceration, cholecystitis and appendicitis cause flatulent dyspepsia because of the associated pyloric spasm. The reason for symptoms in people with sliding hiatus hernia is obviously the loss of the normal acute oesophago-gastric angulation, and it is interesting to note that, with the development of an oesophageal stricture, which physically limits regurgitation, symptoms of flatulence improve. Also sufferers from the less common para-oesophageal hernia do not complain of flatulent dyspepsia, for their acute angle of entry of the oesophagus into the stomach is retained.

CAUSES OF FLATULENT DYSPEPSIA

From this brief consideration of the factors which produce, and those which prevent, gastro-oesophageal regurgitation, the following classification of the causes of flatulent dyspepsia may be made:

1. Conditions associated with *weakening of the resisting sphincter mechanism*:
   - (*a*) Hiatus hernia
   - (*b*) Hypotonicity of muscle and laxity of membrane—as seen in debilitating conditions and senility.

2. Conditions associated with *diminution of the abdominal capacity*
   - (*a*) Obesity
   - (*b*) Pregnancy
   - (*c*) Abdominal tumours
   - (*d*) Gastric distension—gluttony, aerophagy.
   - (*e*) Constricting abdominal garments.

3. Conditions associated with active *increase in the intragastric pressure*
   - (*a*) Pyloric spasm. This is caused by such conditions as peptic ulceration of the duodenum, gall-bladder disease, appendicitis, etc.
   - (*b*) Gastric irritation, caused by dietary indiscretion, etc.

During the course of 1 year, whilst engaged in general surgical duties at the Johannesburg General Hospital, I fully investigated every one of my out-patients who complained of flatulent dyspepsia. There were 72 patients in all. Cholecystitis or cholelithiasis was the cause in 22, duodenal ulcer in 15, hiatus hernia in 9, 'right inguinal fossa' pathology in 7, gastric ulcer in 4, obesity in 5 and ventral hernia in 3; 7 patients were not categorized. Thus, in my experience of hospital patients who suffer from flatulence and indigestion, 30% have gall-bladder disease, 20% duodenal ulcers and 12% hiatus herniae. The symptoms are the same because their basic cause is gastro-oesophageal regurgitation. This is not to say that the various conditions cannot be clinically distinguished; indeed in most instances each condition adds its own peculiar facet to the dyspepsia. With gall-bladder disease the role of fatty foods in the production of dyspepsia and the right hypochondrial pain provide strong clues; with duodenal ulceration, the hunger pains and the relief afforded by food are characteristic; whilst postural intensification of dyspepsia is strongly suggestive of hiatus hernia. However, in all these conditions reflux dyspepsia is not infrequently the major complaint, and the final differentiation must then depend upon special investigations. Of course the vast majority of sufferers accept their discomfort as a more or less normal visitation and are never seen in hospital practice. They are in the general practitioner's own particular domain, for temporary relief is readily afforded by antacids such as Amphogel, Rennie's tablets, bismuth and a host of others. These act by neutralizing the irritating enzymes so that the oesophagus, though still the recipient of stomach contents, gains a temporary respite. If, however, one appreciates the basic factors underlying the complaint, management can be far more confident and effective. Most practitioners readily recognize cases where cholecystitis and peptic ulceration are responsible, for here specific symptoms shout the diagnosis. Hiatus herniation, however, is very frequently treated lightly and, in my series of 92 cases, the average time that elapsed between the onset of symptoms and definitive diagnosis was 12 years. The first duty of the doctor called to advise a patient with habitual dyspepsia is to make a diagnosis and, where a postural history is obtained, a barium meal with abdominal compression or with a Trendelenburg tilt of at least 60° from the horizontal must be done.

Treatment should depend on the cause. An obese patient will be cured by weight reduction and nothing else. A diseased gall-bladder, an ulcerated duodenum, or an abdominal tumour, must be effectively managed. A pregnant woman must wait her delivery, though dietary management, to prevent overeating and gain in weight above that normally expected, will ensure greater comfort. With hiatus herniation the management is a matter of judgment for here, in addition to the disruption of the defensive mechanism, an excessive extruding force, namely obesity, is frequently present. Weight reduction is of great benefit and should be insisted upon even when operation is contemplated. While this is not the place for a discussion of the indications for operation on hiatus herniae, this can be said: Operation will cure the dyspepsia, but it must not be considered by the patient as a licence to indulge the palate and increase the girth.

I must thank the staff of the Photographic Unit of the Department of Medicine, University of the Witwatersrand, for their expert assistance in the preparation of the illustrations. Much of the experimental work summarized here was subvented by a grant from the Council of Scientific and Industrial Research of South Africa.

REFERENCES

Alvarez, W. C. (1948): *Introduction to Gastroenterology*. New York: Hoeber.
Cannon, W. D. (1911): *The Mechanical Factors of Digestion*. London: E. Arnold.
Johnstone, A. S. (1946): Brit. J. Radiol., **19**, 101.
Johnstone, A. S. (1951): J. Fac. Radiol., **2**, 369.
Marchand, P. (1952): Brit. J. Radiol., **25**, 476.
Marchand, P. (1955): Brit. J. Surg., **42**, 504.
Marchand, P. (1957): Thorax, **12**, 189.

SEASONAL VARIATION OF THE INCIDENCE OF MYOCARDIAL INFARCTION IN JOHANNESBURG

PRELIMINARY COMMUNICATION*

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and

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It has been our impression for some time that episodes of myocardial infarction and coronary insufficiency have a higher incidence in winter than in summer. Consequently we inspected the statistical records of the Metropolitan Life Insurance Company of New York[1] and noted a considerably higher death rate from myocardial infarction in winter months (Fig. 1). The highest rate is consistently in January to March which, in the United States, are normally the coldest months of the year, July being the warmest.[2] Studies in the available literature favour a higher winter incidence.[3-12] Several of these studies, however, have concerned themselves with the incidence of myocardial infarction found at necropsy and, as the chances of dying of heart disease may well be higher in winter, such figures may not reflect the true incidence of the disease. For this reason, and because only one previous study has been conducted in the Southern Hemisphere,[8] we decided to investigate the seasonal incidence of myocardial infarction among patients seen by us in private practice in Johannesburg. We regard this investigation as a preliminary observation.

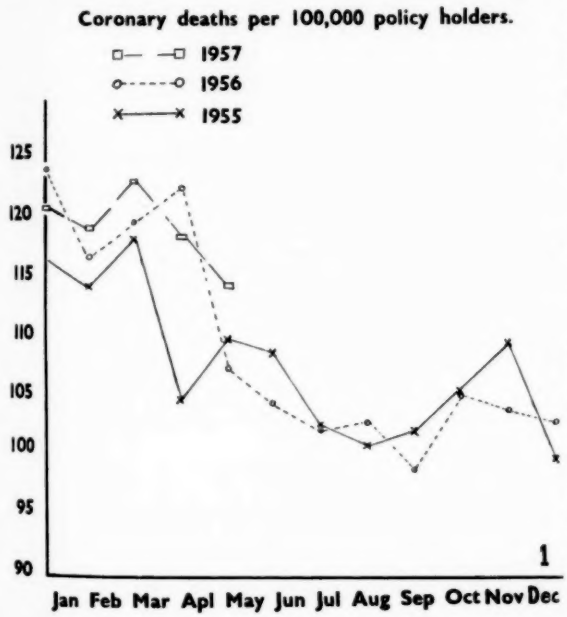

Fig. 1. Graph drawn from figures abstracted from Statistical Bulletin of Metropolitan Life Insurance Co.[1]

* A paper presented at the South African Medical Congress, Durban, September 1957. An article on similar investigations in Cape Town will be found at page 429 of this issue (see letter from Dr. Nellen, National Chairman, S.A. Cardiac Society, on page 436).

Methods

All the patients experiencing myocardial infarction between September 1953 and May 1957 inclusive have been studied. They fall into the following three groups:

1. Those with the classical clinical picture and electrocardiographic evidence of 'through and through' infarction.

2. Those with the classical clinical picture and other ancillary evidence of infarction, e.g. pyrexia, raised ESR or raised serum glutamic oxaloacetic transaminase (SGO-T), but with electrocardiograms not showing pathological Q waves. The electrocardiograms have shown ST-T changes of 'subendocardial' or 'subepicardial' infarction.[13]

3. Two patients with the classical clinical picture and markedly raised SGO-T, but with atypical electrocardiographic changes.

The number of episodes of myocardial infarction occurring each month was expressed as a percentage of the total number of all new patients seen by us in each month, thus allowing for the 'vagaries' of private practice, and for vacations on the part of patient and doctor.

The number of deaths occurring within the first fortnight of infarction was estimated.

Results

There were 228 episodes of myocardial infarction among a total 3,652 new patients, giving an incidence of 6·2%.

The monthly breakdown of these figures is shown in Table I and the monthly incidence is illustrated in Fig. 2.

TABLE I. MONTHLY INCIDENCE OF CASES OF MYOCARDIAL INFARCTION

Year	Month	M.I.	New Cases	M.I./New Cases (%)
1953 ..	September	3	27	11·1
	October ..	0	45	0
	November ..	2	52	3·8
	December ..	1	8	
1954 ..	January ..	5	58	8·6
	February ..	5	56	8·9
	March ..	3	77	4·0
	April ..	6	70	8·6
	May ..	3	48	6·3
	June ..	7	77	9·1
	July ..	3	65	4·6
	August ..	5	78	6·4
	September ..	2	48	4·2
	October ..	4	74	5·4
	November ..	1	87	1·1
	December ..	7	78	8·9
1955 ..	January ..	1	68	1·5
	February ..	2	69	2·9
	March ..	6	87	6·9
	April ..	2	44	4·5
	May ..	6	99	6·2
	June ..	12	80	15·0
	July ..	7	64	10·9
	August ..	9	103	8·7
	September ..	9	82	11·0
	October ..	7	92	7·6
	November ..	4	107	3·7
	December ..	2	57	3·5
1956 ..	January ..	3	80	3·8
	February ..	2	90	2·2
	March ..	4	109	3·7
	April ..	6	91	6·6
	May ..	4	76	5·3
	June ..	10	121	8·3
	July ..	6	99	6·0
	August ..	5	133	3·9
	September ..	5	112	4·5
	October ..	8	124	6·5
	November ..	10	111	9·0
	December ..	9	79	11·4
1957 ..	January ..	6	131	4·6
	February ..	4	106	3·8
	March ..	8	119	6·7
	April ..	7	75	9·3
	May ..	7	96	7·3
	Total	228	3,652	6·2

M.I. = Myocardial Infarctions.

For the purposes of comparing 'summer' and 'winter' incidence, the period under review was divided into 4 completed summer periods (October to March inclusive) and 3 completed winter periods (April to September inclusive). The distribution of the episodes in these periods is shown in Table II.

TABLE II. 'WINTER' AND 'SUMMER' INCIDENCE OF CASES OF MYOCARDIAL INFARCTION

		M.I.	New Cases	M.I./N.C. (%)
Summer Seasons	Oct. 53-Mar. 54 ..	16	296	5·4
	Oct. 54-Mar. 55 ..	21	463	4·5
	Oct. 55-Mar. 56 ..	22	535	4·1
	Oct. 56-Mar. 57 ..	45	670	6·7
	Total ..	104	1,964	5·3
Winter Seasons	Apr.-Sept. 54 ..	26	386	6·7
	Apr.-Sep. 55 ..	45	472	9·5
	Apr.-Sep. 56 ..	36	632	5·7
	Total ..	107	1,490	7·18
Total		211	3,454	6·1

M.I. = Myocardial Infarctions.

In the 'summer' periods there were 104 episodes amongst 1,964 new patients, giving an incidence of 5·3%. In the 'winter' periods there were 107 episodes amongst 1,490 new patients, an incidence of 7·18%. The application of standard tests suggests that the difference in incidence (1·88%) is 'significant at the 5% level'.

The 228 episodes were experienced by 211 patients, 13 patients had 2 attacks and 2 patients had 3 attacks during the period under review. There were 20 deaths within a fortnight of the attack—a mortality of 8·9%.

DISCUSSION

A major difficulty in assessing the seasonal incidence of myocardial infarction is the assessment of the 'population at risk'. This difficulty occurs both in hospital and private practice but perhaps to a greater degree in the latter. It was felt, however, that a calculation of the number of myocardial infarctions as a percentage of the total number of new patients seen each month would to some extent overcome the difficulty for the following reasons:

1. Allowance is made for (*a*) vacations by the doctor and patients and (*b*) increasing 'size' of practice.

2. There is no reason to suppose any alteration in the type of cases seen by specialist physicians in private practice.

A criticism of this method is that the actual 'population at risk' is progressively greater with the advance of time than is reflected by the number of new patients seen, as old patients to the practice are also at risk. However, by calculating the seasonal incidence of the whole period, this difficulty is probably overcome, since it will equally affect both 'summer' and 'winter' seasons.

Fig. 2 indicates that the presented seasonal difference is weighted by a high 'winter' incidence in 1955, with a low incidence in the subsequent 'summer'. However, even excluding these 2 periods, the winter incidence is found to be 0·4% higher. Although this is certainly not statistically significant, it follows the same trend. Moreover, if one considers *all* the months reviewed (including the 3 extra 'winter' months, September 1953 and April and May 1957) one finds that in 14 out of 21 'winter' months (66·6%) the incidence exceeds the average incidence for the whole period. In only 9 out of 23 'summer' months (39%) does this apply (Fig. 2). Again, excluding the 'winter' of 1955 and the subsequent 'summer', the figures are less impressive, but nevertheless show the same trend i.e. 9 out of 15 'winter'

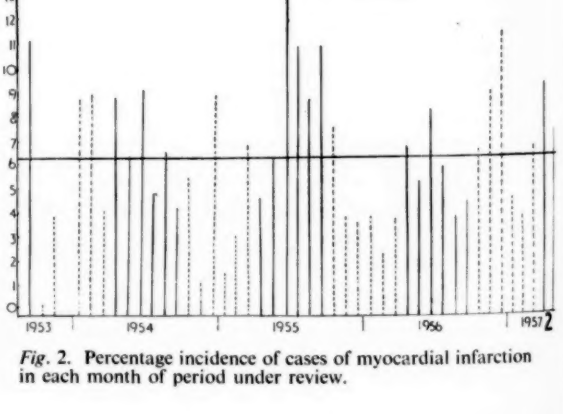

Fig. 2. Percentage incidence of cases of myocardial infarction in each month of period under review.

months (60%) exceed the average, compared with 8 out of 17 'summer' months (47%).

Over the whole period (i.e. including the extra 3 winter months) but excluding the 'winter' of 1955 and the subsequent 'summer', the 'winter' incidence of 6·5% exceeds the 'summer' incidence of 5·7%.

The greater winter incidence would be less impressive if the year was divided into a winter period from June to November and a summer period from December to May. However, we felt justified in dividing the year into 'winter' and 'summer' as stated, as difference between the winter and summer mean temperatures (maximum and minimum) is greater with this division than with the former.* It is of interest too that this method of dividing the year includes the months of greater average rainfall in the summer periods.

A survey of the available literature indicates that the great majority of authors found a higher winter incidence.[1,3-12] One group [14] found a higher summer incidence, but later [15] reported an increased frequency during periods of sudden inflow of both polar air and tropical air masses. Another group,[10] although believing that seasonal incidence was not important, stated: 'There is a slight tendency for more attacks to occur in the winter months.' Their statement that 'it is likely that the seasonal variation reported by others is to a large extent due to summer migration from the large communities on the part of susceptible persons' is not applicable to our series for the previously mentioned reasons. Miller *et al.*[16] and Master and Jaffe[17] noted no *striking* difference in the frequencies of myocardial infarction in any one season as compared with another. However, both groups showed a higher winter incidence in their published figures.

Master *et al.*[18] concluded that there was no significant seasonal variation, but Rosahn[9] analysed their figures by subdividing the year in a different way, and showed a highly significant difference with winter incidence predominant.

Lewitus and Neuman[19] found no significant difference between summer and winter incidence; in their series they showed that the incidence of myocardial infarction followed a Poisson distribution. The only previous study from the southern hemisphere[8] showed a higher winter incidence, but did not, in the figures presented, differentiate between myocardial infarction and left ventricular failure.

Thus, on the whole, there is good evidence for a higher winter incidence of myocardial infarction. However, in several series the figures concern *deaths* due to myocardial infarction, which might reflect a greater *severity* of heart disease in winter rather than a higher *incidence* of myocardial infarction. Our figures indicate an actual higher winter incidence and, if this can be substantiated by further analyses of much larger series, including hospital cases, there may be some justification for following the advice of Evan Bedford[3] to send 'potential cases to winter in warmer climates'.

* Calculated from figures supplied by the Parks and Recreation Department of the City of Johannesburg.

SUMMARY

The seasonal incidence of myocardial infarction in a series of private patients in Johannesburg is analysed. It is demonstrated that there is a higher winter incidence, and standard tests suggest that the difference is 'significant at the 5% level'.

We thank Prof. J. E. Kerrich, of the Department of Mathematics of the University of the Witwatersrand, for a statistical analysis of our figures and Mr. C. Shepherd, of the Parks and Recreation Department of the City of Johannesburg, for supplying meteorological data. Mr. A. M. Shevitz is thanked for the reproduction of the figures.

REFERENCES

1. Statistical Bulletin, Metropolitan Life Insurance Company, New York (1955-1957): Vols. 36-38.
2. Ekblau, W. E. (1951): The United States of America, Encyclopaedia Britannica, 40th ed., 1951 printing, vol. 22, p. 728.
3. Bedford, D. E. (1939): Lancet, **1**, 634.
4. Cohn, A. E. (1926): Amer. Heart J., **2**, 275.
5. Bean, W. B. (1937): *Ibid.*, **14**, 684.
6. Bean, W. B. and Mills, C. A. (1938): *Ibid.*, **16**, 701.
7. Bundesen, H. N. and Falk, I. S. (1926): J. Amer. Med. Assoc., **87**, 1987.
8. Ritchken, J. (1946): M.D. Thesis, University of Witwatersrand.
9. Rosahn, P. D. (1937): J. Amer. Med. Assoc., **109**, 1294.
10. Mintz, S. S. and Katz, L. N. (1947): Arch. Intern. Med., **80**, 205.
11. Mills, R. A. (1953): J. Amer. Med. Assoc., **153**, 910.
12. Wood, F. C. and Hedley, O. F. (1935): Med. Clin. N. Amer., **19**, 151.
13. Levine, S. A. (1951): *Clinical Heart Disease*. Philadelphia: W. B. Saunders Co.
14. Heyer, H. E., Teng, H. C. and Barris, W. (1953): Amer. Heart J., **45**, 741.
15. Teng, H. C. and Heyer, H. E. (1955): *Ibid.*, **49**, 9.
16. Miller, R. D., Burchell, H. B. and Edwards, I. E. (1951): Arch. Intern. Med., **88**, 597.
17. Master, A. M. and Jaffe, H. L. (1952): J. Amer. Med. Assoc., **148**, 794.
18. Master, A. M., Dack, S. and Jaffe, H. L. (1937): *Ibid.*, **109**, 546.
19. Lewitus, Z. and Neuman, J. (1957): Amer. Heart J., **53**, 339.

THE SEASONAL INCIDENCE OF CARDIAC INFARCTION AT GROOTE SCHUUR HOSPITAL, CAPE TOWN*

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During the past few decades the effect of weather conditions on the incidence of cardiac infarction has been the subject of several studies, particularly in the USA. Opinion in general has been that there is a higher incidence in cold weather. Thus, figures published from New York,[1,2] Boston,[3-5] Philadelphia,[6] Pittsburgh,[7] Cincinatti,[8] Chicago[9] and Rochester[10] support this contention. Even in the temperate areas which correspond to our local conditions in Cape Town such as Los Angeles[11] and Nashville, Tennessee,[12] a higher incidence in the winter months has been recorded. Only in Dallas, Texas,[13] has the reverse been reported and in a later paper this discrepancy has been attributed to sudden inflows of polar and of tropical air masses.[14] In London[15] an increased incidence in cold weather has also been reported, whereas in Israel[16] weather conditions appeared to have no effect on the incidence.

* An article on similar investigations in Johannesburg will be found at page 427 of this issue (see letter from Dr. Nellen, National Chairman, S.A. Cardiac Society, on page 436).

This study was stimulated by a preliminary report from Johannesburg by Bradlow and Zion[17] on an increased incidence of cardiac infarction in that city during the cold months of the year and reported in more detail later.[18] The incidence of this disease in Cape Town over a comparable period was, therefore, investigated.

MATERIAL AND METHODS

The electrocardiographic service of the Cardiac Clinic during the period under survey (1952-56) included all in-patients and out-patients attending Groote Schuur Hospital and the 44 in-patient teaching beds of the New Somerset Hospital. In the former hospital there are 854 beds and approximately equal numbers of European and non-European patients are treated. As there is a means test, the poorer section of the European community only are permitted to attend, but this does not affect the non-European attendance. The incidence and seasonal variation of infarction as shown by our figures therefore apply to those sections of the community that are relatively underprivileged and do not necessarily correspond to the total population of Cape Town. There is no reason, however, to believe that the more privileged members of the community behave differently.

The first group of patients studied was obtained from the files of the anticoagulant service of the hospital. The patients receiving long-term anticoagulant therapy for coronary vascular disease were re-examined in the Cardiac Clinic, including electro-cardiography and roentgenoscopy, and their case histories were reviewed. The practice of long-term anticoagulant therapy only became generally used in the hospital in 1955, so that in the 12 months of 1954 there were only 19 cases, whereas in 1955 and 1956 there were 60 and 46 cases respectively, the total number therefore being 125. It must be accepted that this is a specially selected group, but the selection does not appear to depend upon the weather. Patients suffering from angina pectoris without a clear story of infarction were excluded from this study.

The second group of patients was selected from the electrocardiographic records in the Cardiac Clinic over a 4-year period from January 1952 to December 1955. Any patient suspected of having coronary vascular disease in this hospital automatically had an electro-cardiogram taken and all tracings were examined by the author. The electrocardiographic records were classified in 3 groups as follows:

Type 1. Electrocardiograms showing the classical pattern of infarction.[19] Thus, in anterior infarction wide or deep Q waves in the praecordial leads (V1-V7), or diminution in the R waves across the praecordium, were required in addition to T wave inversion or ST segment change. In posterior infarction a Q wave of at least 0·04 seconds in width or a Q wave deeper than 30% of the R wave in AVF was accepted. In the presence of right bundle-branch block a Q wave of 0·04 seconds in AVF or abnormally wide Q waves in the praecordial leads were held to indicate infarction. Infarction was seldom diagnosed in the presence of left bundle-branch block unless a Q wave or gross ST segment depression over the left ventricle were present. There were 621 patients in this group.

Type 2. Electrocardiograms taken from patients with a clinical history of angina pectoris or cardiac infarction, showing T wave inversion without Q waves over the antero-lateral or posterior aspects of the left ventricle, or bundle-branch block without significant Q waves (20). There were 534 patients with this type of pattern.

Type 3. Electrocardiograms which were normal at rest from patients with an undoubted story of coronary vascular disease often confirmed by positive effort tests. There were 58 such patients.

Thus in the 3 groups there were 1,213 patients. As it was not possible to examine the files of all 1,213, a sample of each was made as follows. All those patients who appeared on the files of the anticoagulant therapy service of the hospital as having received anticoagulant therapy, whether short- or long-term, were reviewed. There were 239 with Type-1, 69 with Type-2 and 9 with Type-3 electrocardiographic patterns. The remainder were selected at random, the determining factor being the ability of the hospital records department to find the appropriate record. Of the 621 patients showing a Type-1 electrocardiographic pattern 543 were analysed and of the 534 showing Type-2 pattern 230 were analysed. All 58 of Type 3 were analysed. The sample, therefore, consisted of 831 of the 1,213 cases.

For the purpose of this study only cases with episodes of prolonged pain suggestive of cardiac infarction were selected for study from these 831 cases. There were 23 cases of angina pectoris who were, therefore, excluded. The month of the year when each patient developed the acute prolonged attack of pain was recorded wherever possible, but in 16 this was not known, leaving 792 cases for analysis. In a few cases, the date of a second infarction only was known. Recurrent infarctions were considered separately. The total number of cases analysed, therefore, was 792 first infarctions and 95 recurrent infarctions.

RESULTS

In Table I is shown the monthly incidence of first infarctions in 792 cases (European and non-European) during the 4 years 1952-55; in Table II the monthly incidence up to December 1957 of all the 887 infarctions in the same 792 cases; and in Table III the monthly incidence of first infarctions in the 125 cases (all races) receiving long-term anticoagulant therapy during the 3 years 1954-56. In Table IV is shown the monthly

TABLE I. MONTHLY INCIDENCE OF FIRST INFARCTIONS IN 792 CASES SEEN IN 4 YEARS 1952-55

ECG Type	*Race*	*Jan.*	*Feb.*	*Mar.*	*April*	*May*	*June*
1	European	26	26	35	25	32	44
	Non-European	12	7	10	15	8	28
2 and 3	European	7	8	14	16	13	13
	Non-European	5	4	10	3	5	5
Total	European	33	34	49	41	45	57
	Non-European	17	11	20	18	13	33
	All Races	50	45	69	59	58	90

ECG Type	*Race*	*July*	*Aug.*	*Sept.*	*Oct.*	*Nov.*	*Dec.*
1	European	38	40	43	33	42	27
	Non-European	5	7	16	7	7	10
2 and 3	European	17	15	24	12	10	17
	Non-European	10	8	9	12	9	3
Total	European	55	55	67	45	52	44
	Non-European	15	15	25	19	16	13
	All Races	70	70	92	64	68	57

TABLE II. MONTHLY INCIDENCE TO DATE OF 887 INFARCTIONS IN 792 CASES SEEN IN 4 YEARS 1952-55

ECG Type	Race	Jan.	Feb.	Mar.	April	May	June
1	European	31	30	40	33	37	49
	Non-European	12	9	11	15	8	31
2 and 3	European	7	10	14	18	13	18
	Non-European	5	4	10	3	5	5
Total	European	38	40	54	51	50	67
	Non-European	17	13	21	18	13	36
	All Races	55	53	75	69	63	103

ECG Type	Race	July	Aug.	Sept.	Oct.	Nov.	Dec.
1	European	46	47	49	36	48	31
	Non-European	5	7	16	8	8	11
2 and 3	European	17	20	26	14	11	18
	Non-European	10	8	9	12	9	3
Total	European	63	67	75	50	59	49
	Non-European	15	15	25	20	17	14
	All Races	78	82	100	70	76	63

TABLE III. MONTHLY INCIDENCE OF FIRST INFARCTIONS IN 125 CASES ON LONG-TERM ANTICOAGULANT THERAPY IN 3 YEARS 1954-56

Jan.	Feb.	Mar.	Apr.	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
11	12	8	10	10	13	10	12	16	11	0	12

TABLE IV. THE MONTHLY INCIDENCE OF 339 DEATHS FROM ALL CAUSES IN 877 PATIENTS WITH CORONARY VASCULAR DISEASE

ECG Type	Race	Jan.	Feb.	Mar.	April	May	June
1	European	11	12	16	9	14	17
	Non-European	4	2	5	3	8	7
2	European	2	5	3	3	5	4
	Non-European	3	1	0	2	4	4
3	European	0	0	1	0	0	2
	Non-European	1	0	0	0	1	0
Total	European	13	17	20	12	19	23
	Non-European	8	3	5	5	13	11
	All Races	21	20	25	17	32	34

ECG Type	Race	July	Aug.	Sept.	Oct.	Nov.	Dec.
1	European	18	17	17	21	17	17
	Non-European	5	6	8	4	5	5
2	European	6	3	7	14	0	3
	Non-European	3	1	2	1	1	4
3	European	1	0	0	2	1	0
	Non-European	0	0	0	0	0	1
Total	European	25	20	24	37	18	20
	Non-European	8	7	10	5	6	10
	All Races	33	27	34	42	24	30

incidence of the 339 deaths from all causes in all the 877 cases examined in this survey. For the purpose of this analysis the date of the onset of the disease is not relevant; Table IV therefore includes the 831 cases analysed in 1952-55 and the 46 cases on long-term anticoagulants in 1956 and subsequently.

DISCUSSION

The results in Tables I, II and III show a significant seasonal difference in the incidence of myocardial infarction in Cape Town. Thus, if one divides the year into 'summer' and 'winter', as Bradlow and Zion[18] have done in their Johannesburg analysis, the first attack of myocardial infarction (Table I) occurred in 353 cases in the 'summer' (6 months October to March), and in 439 cases in the 'winter' (6 months April to September). If all the episodes of infarction are included (Table II), the incidence in 'summer' was 392 cases and in 'winter' 495 cases.

The seasons are not quite identical at Cape Town and Johannesburg. At Cape Town the climatic conditions can be more correctly described as 'summer' (4 months December to March), 'winter' (4 months June to September) and 'between seasons' (October, November, April and May)*. If this seasonal division is adopted, the number of first infarctions (Table I) in 'summer' is 221 and of all the episodes of infarction (Table II) 246; in 'winter' the figures are 322 and 363 and in 'between seasons' 249 and 278. The survey is over a period of 4 years and the differences are statistically significant for both racial groups.

The 831 cases analysed represent a statistically significant sample of the 1,213 cases of coronary vascular disease recorded in the Groote Schuur Hospital during the 4 years 1952-56. The findings are essentially the same for both racial groups whether the cases were selected on purely electrocardiographic criteria (Type 1) or on clinical criteria (Types 2 and 3). They can be assumed to represent the seasonal incidence of the disease as it occurred in Groote Schuur Hospital during these 4 years. The 'population at risk', particularly the European, fluctuates considerably, as Cape Town is an important port and a summer resort. Thus, during 1956 it is estimated[21] that there were 220,000 visitors to the city and 120,000 are regarded as having been present during December, January and February. Even taking into consideration the fact that many of the visitors belong to an income group which is officially debarred from attending the hospital, the population which the hospital drains is larger in summer than in winter. Not only is the population movement towards Cape Town in the summer but there is an exodus from Cape Town during the wet winter months. In view of these population fluctuations, there is added significance in the fact that more infarcts are recorded in winter than in summer.

It is therefore of interest to analyse where the visitors were domiciled: 81 cases were found who lived out of Cape Town with an incidence of 28 infarctions in 'summer', 22 in 'winter' and 31 in the 'between seasons'. The race particularly involved was the European.

When the data obtained from the 125 patients (1954-56) receiving long-term anticoagulant therapy (Table III) is studied, the results are essentially the same. Thus, there were 54 cases of infarction in 'summer' and 71 in 'winter', dividing the year according to Bradlow and Zion,[18] or 31 in 'summer', 51 in 'winter' and 43 in 'between seasons', according to the method suggested in this study. For this very selected group of cases the results obtained are similar to those shown in Tables I and II, though the difference is not statistically significant.

The findings are in keeping with figures published by the majority of authors elsewhere.[1-12,15,22-26] In some of the series the data were obtained from necropsy material and therefore reflect deaths from cardiac infarction, in others the material was obtained from clinical experience. Analysis of the

* The average mean temperature in degrees Centigrade during the 5 years 1952-56, as supplied by the Metrological Department of the Royal Observatory, Cape Town, supported this arrangement of the seasons. Thus in 'summer', i.e. 4 months December to March, the temperatures were 19·8, 21·9, 21·5 and 20·5°C; in 'winter', i.e. 4 months June to September, they were 13·5, 12·4, 12·9 and 14·9°C; in 'between seasons', i.e., October, November, April and May, they were 15·5, 19, 17·2 and 15·2°C. The average mean rainfall in inches over the same 5-year period was as follows: 'summer' 0·9, 0·2, 0·9 and 0·6; 'winter' 3, 5, 4·3 and 1·9; 'between seasons' 1·5, 1·2, 2·8 and 4·8.

clinical data in this study strongly supports the view that the incidence of infarction is higher in the winter than in the summer.

Analysis of our series of deaths (Table IV) supports the clinical findings. Of the original 877 patients analysed, 42 cases could at no time be traced. Since 1956 a further 26 Europeans and 43 non-Europeans were lost sight of. Information is available to date on the remaining 766 patients; amongst these there have been 339 deaths. In a few cases death was due to causes unassociated with the heart, but in the great majority cardiac infarction was recorded as the cause of death. The information was generally obtained from the practitioner in charge of the case or the relatives. Both immediate deaths and death many years after the onset of the disease were included. There were 163 deaths in 'summer' and 177 in 'winter', dividing the year according to Bradlow and Zion,[18] or 96 in 'summer', 128 in 'winter' and 115 in 'between seasons', as used in this study. The incidence of death in cases of cardiac infarction is, therefore, also higher in the winter than in the summer months.

Lastly, although the incidence of this disease is far greater in the European than in the non-European[19,20] the same seasonal variation is seen in the two racial groups.

SUMMARY

1. The seasonal incidence of cardiac infarction in 792 patients seen at Groote Schuur Hospital during the 4 years 1952-55 is analysed.

2. There is no difference in seasonal variation between European and non-European patients.

3. The seasonal incidence of cardiac infarction in 125 patients at Groote Schuur Hospital during the 3 years 1954-56 receiving long-term anticoagulant therapy is also analysed.

4. There is a statistically significant increased incidence of the disease in the winter months as compared with the summer. The incidence in 'between seasons' lies between the winter and summer incidence.

5. The seasonal incidence of deaths in 877 patients suffering from coronary vascular disease is also analysed.

6. The seasonal incidence of deaths parallels the clinical incidence of the disease.

I wish to thank Dr. C. Merskey for putting the files of the anticoagulant service at my disposal and for his help with the statistical analysis. My special thanks are due to Dr. J. Prisman for his unceasing help and interest in the development of the Cardiac Clinic. Mrs. C. Hall gave invaluable assistance in the analysis of the data and follow-up of the patients investigated. I also wish to thank the City Council of Cape Town and the Council for Scientific and Industrial Research for their financial assistance in this investigation.

REFERENCES

1. Master, A. M., Dack, S. and Jaffe, H. L. (1937): J. Amer. Med. Assoc., **109**, 546.
2. Master, A. M. and Jaffe, H. L. (1952): *Ibid.*, **148**, 794.
3. Bean, W. B. (1937): Amer. Heart J., **14**, 684.
4. Wolff, L. and White, P. D. (1926): Boston Med. Surg. J., **195**, 13.
5. White, P. D. (1926): J. Amer. Med. Assoc., **87**, 1525.
6. Wood, F. C. and Hedley, O. F. (1935): Med. Clin. N. Amer., **19**, 151.
7. Mullins, W. L. (1936): Pennsylvania Med. J., **39**, 322.
8. Bean, W. B. and Mills, C. A. (1938): Amer. Heart J., **16**, 701.
9. Mintz, S. S. and Katz, L. N. (1947): Arch. Intern. Med., **80**, 205.
10. Miller, R. D., Burchell, H. B. and Edwards, J. E. (1951): *Ibid.*, **88**, 597.
11. Hoxie, H. J. (1940): Amer. Heart J., **19**, 475.
12. Billings, F. T., Kalstone, B. M., Spencer, J. L., Ball, C. O. T. and Meneely, G. R. (1949): Amer. J. Med., **7**, 356.
13. Heyer, H. E., Teng, H. C. and Barris, W. (1953): Amer. Heart J., **45**, 741.
14. Teng, H. C. and Heyer, H. E. (1955): *Ibid.*, **49**, 9.
15. Bedford, D. E. (1939): Lancet, **1**, 634.
16. Lewitus, Z. and Neumann, J. (1957): Amer. Heart J., **53**, 339.
17. Bradlow, B. A. and Zion, M. M. (1957): S. Afr. Medical Congress, Durban.
18. *Idem* (1958): S. Afr. Med. J., **32**, 427.
19. Vogelpoel, L. and Schrire, V. (1955): Lancet, **2**, 1108.
20. Schrire, V. (1958): S. Afr. Med. J., **32**, 177.
21. Visitors' Bureau, Cape Town.
22. Statistical Bulletin Metropolitan Life Insurance Company, vols. 36-38, 1955-57.
23. Cohn, A. E. (1926): Amer. Heart J., **2**, 275.
24. Bundesen, H. N. and Falk, I. S. (1926): J. Amer. Med. Assoc., **87**, 1987.
25. Rosahn, P. D. (1937): *Ibid.*, **109**, 1294.
26. Mills, R. A. (1953): *Ibid.*, **153**, 910.

UNIVERSITEIT VAN PRETORIA

By die promosieplegtigheid op 29 Maart 1958 is die volgende grade en medaljes toegeken:

Graad van Baccalaureus in Geneeskunde en Snykunde

Bekker, Johannes Hendrik.
Bonnet, Wessel Johannes Badenhorst.
Botha, Gerhardus, Johannes Beukes.
Crous, Jacobus Johannes.
de Beer, Jacobus Johannes Cornelius.
de Beer, Laurie.
de Swardt, Hendrik Frederik.
de Villiers, Johanna Francina.
de Villiers, Pieter Kuyper.
Erasmus, Jan Abraham.
Faurie, Jacques Pierre.
Graham, Andries Frederik.
Hamersma, Teertse.
Jansen, Laurens.
Kachelhoffer, Rudolf Johannes Francois.
Kallmeyer, Jeffrey Cedric.
Keevy, Clyde Matthew.
Lindeque, Willem Johannes Marthinus Petrus.
Lombard, Nimrod Mason.
Maree, Johanna Susanna.
McGill, Douglas John.
Naude, Marthinus Christoffel.
Nel, Gerhardus Christiaan.
Nel, Philippus Johannes Cornelis.
Opperman, Johannes Marthinus.
Pretorius, Hercules Albertus.
Pretorius, Jan Jacobus, Stephanus.
Reisner, Salomon Herz.
Schoeman, Petrus Frederik Cornelius.
Schoeman, Stephanus Johannes.
Schoonees, Johann August.
Serfontein, Jacobus Hendrik.
Siegrühn, Gert Cornelius.
Snyman, Johan Daniel.
Steyn, Johannes Christoffel.
van der Merwe, Schalk Willem.
van Rensburg, Wessel Hendrik Janse.
van Rooyen, Johan Christiaan.
Venter, Johannes Lodewikus.
Visser, Ernestus Jacobus.
Zöllner, Werner Bruno.

Graad van Magister in Geneeskunde

Barnard, Beatrix. (Dept. Anestesiologie.)
Blake, Tower. (Dept. Interne Geneeskunde.)
Cockcroft, Colin Royden. (Dept. Pediatrie.)
de Villiers, Louis Scholtz. (Dept. Patologie.)
Henkel, Irmin. (Dept. Chirurgie.)
Jacobs, Johannes Jacobus Daniel. (Dept. Chirurgie.)
Snyman, Giles Wynand. (Dept. Interne Geneeskunde.)
Truter, Petrus Johannes. (Dept. Anestesiologie.)
van Rensburg, Barend Gerhardus Janse. (Dept. Anestesiologie.)
Viljoen, Michiel Francois. (Dept. Interne Geneeskunde.)
Zaaiman, Ignatius Michael. (Dept. Chirurgie.)

Horace Wells-medalje. Vir die student wat die hoogste punte in Anestesiologie in die eksamen van die vyfde jaar van die M.B., Ch.B.-kursus behaal het: Pretorius, Hercules Albertus.

L. J. te Groen-medalje vir Obstetrie en Ginekologie. Vir die finale jaar M.B., Ch.B.-student wat die beste in Obstetrie en Ginekologie presteer het: de Beer, Laurie.

Protea Holdings-pryse. (i) Vir die beste finale jaar student in Radiologie: Jansen, Laurens. (ii) Vir die beste finale jaar student in Interne Geneeskunde: Opperman, Johannes Marthinus.

PASSING EVENTS : IN DIE VERBYGAAN

Dr. Pericles Menof of Johannesburg has been invited to represent South Africa at the Fifth International Congress of Internal Medicine to be held at Philadelphia on 23-26 April 1958. He will be away for about 3 months, during which time he will take the opportunity of visiting various North American clinics.

Dr. Pericles Menof van Johannesburg is uitgenooi om Suid Afrika te verteenwoordig op die 5de Internasionale Kongres van Interniste wat gehou sal word 23-26 April 1958 te Philadelphia. Hy sal afwesig wees vir 'n periode van naasteby drie maande en is van plan om van die geleentheid gebruik te maak om verskeie Noord-Amerikaanse klinieke te besoek.

* * *

E. & S. Livingstone Ltd. Mr. Charles Macmillan, Managing Director of E. & S. Livingstone Ltd., Medical, Scientific, Nursing and Dental Publishers, Edinburgh, is visiting South Africa shortly. His itinerary will be as follows: 21-25 April, Salisbury, S.R. (at Meikle's Hotel); 2-6 May, Johannesburg (at the Langham Hotel); 6-11 May, Durban (at the Marine Hotel); 16-23 May, Cape Town (at the Queen's Hotel, Sea Point).

* * *

Red Cross War Memorial Children's Hospital, Rondebosch, Cape. The next meeting in the Postgraduate Seminar Series of lectures under the auspices of the University of Cape Town Department of Child Health will be held in the lecture theatre of this Hospital on Wednesday 7 May at 5 p.m. Speakers: Dr. R. van der Riet, 'Physiological Aspect of Bowel-function', and Dr. I. G. Sacks, 'Intussusception'. All medical practitioners are welcome.

* * *

The Second World Congress on Medical Education is to be held in Chicago, USA from 30 August to 4 September 1959. Reference was made to the Conference in this *Journal* on 20 October 1956 (**30**, 1021) and 16 February 1957 (**31**, 158). It is announced that the theme of the Conference will be 'Medicine—A Lifelong Study', which is a logical sequel to the 1953 London Conference, at which undergraduate medical education was discussed. One of the basic aims of the Conference is to promote efficient aid to every doctor in increasing his knowledge of medical science concomitantly with modern advances. The scope of the programme will include specialist training, the development of teachers and investigators, and means by which the practitioner can avail himself of the newest findings for use in the medical care he gives his patients. Appromimately 100 invited speakers from more than 50 countries will present papers at the Conference. Simultaneously translation for English, Spanish and French will facilitate the discussions. Further information can be obtained from The World Medical Association, 10 Columbus Circle, New York, 19, N.Y., USA.

* * *

The Westdene Products Scholarships for 1958 have been awarded to the following medical students:

Cape Town University. B. M. Kennelly, 6th year. D. J. Clain, 5th year. A. D. Ginsburg, 4th year.

Natal University. I. M. Seedat, 6th year. B. R. Maku and Miss S. Reddy, 5th year. Miss R. Pather and D. R. de Wahl Matlhoke, 4th year.

Pretoria University. G. J. Pistorius, 6th year. R. E. van Schalkwyk, 5th year. A. van Dam, 4th year.

Witwatersrand University. G. Kos, 6th year. Miss D. Hack, 5th year. A. H. Rubenstein, 4th year.

Three scholarships, valued at £100 each, are awarded annually to 4th, 5th and 6th year medical students at each University in the Union with a medical faculty.

The Westdene Products Scholarship for Pharmaceutical Study, Research and Development for 1958 has been awarded to Mr. C. H. Price, Head of the Pharmacy Department of Rhodes University. Mr. Price will undertake research into the history of pharmacy in South Africa, with special emphasis on pharmaceutical legislation. £200 per annum is made available for this scholarship.

The Westdene Products Nursing Scholarship for Industrial and Scientific Investigation for 1958 has been awarded to Miss R. Alford, Tutor Sister, Carinus Nurses' Training College, Cape Town. This Scholarship is valued at £200 per annum.

THE LATE DR. KURT COLSEN *

Mr. William Girdwood (R.M.), F.R.C.S., of Johannesburg writes: It has been a privilege to have been associated with such a colleague as Kurt Colsen.

Coming to South Africa in 1936 with the background of Sauerbruch and Bohler it follows that he left his mark in the treatment of fractures. His book on fractures is today a standard text-book in countries far beyond our shores.

As a man he had many friends. His love of life, his hospitality, his interests in carpentry, antiques, music and art, travel, chess and cooking endeared him to all who knew him.

By service to his colleagues as Secretary of the Association of Surgeons Group of the Medical Association he played a major part in negotiations on W.C.A. and Medical Aid matters. His medico-legal opinions and advice were sought by the best legal brains in the country and as a surgeon on the Johannesburg Hospital for almost 20 years he will be sorely missed by patients, students and fellow surgeons.

He overcame many difficulties. His war-time service, his obvious teaching abilities and his reliability have established his position in our hearts as a loved South African and a genuine fellow.

* An In Memoriam article and portrait were published in last weeks' *Journal*, page 412.

NEW PREPARATIONS AND APPLIANCES : NUWE PREPARATE EN TOESTELLE

CARBONET—A NEW NON-ADHERENT DRESSING

Smith & Nephew (Pty.) Ltd. introduce Carbonet and supply the following information:

Carbonet, a new type of non-adherent dressing produced by Smith & Nephew Ltd. is a modified form of Jelonet in which the conventional petroleum jelly mass has been replaced by a water-soluble mass composed of a mixture of polyethylene glycols.

Carbonet has many advantages over the conventional paraffin gauze dressing B.P.C. (*tulle gras*), and one of its most important features is the fact that wounds do not become macerated beneath it and healing is not thereby retarded. It has been given an extensive clinical trial in 11 centres in the UK, and has proved itself to be a first class dressing. All the surgeons concerned were unanimous in their approval, and considered that it was better than paraffin gauze dressing B.P.C. in all respects. The following two reports are typical of the trials.

The first one comes from the Casualty Department of the St. Albans City Hospital, Hertfordshire: 'Carbonet was used in more than 20 cases for the treatment of abrasions, both clean

and infected, scalds, burns and for other open wounds such as the nail bed following nail removal. The impressions given of its properties compared with paraffin gauze were as follows: (1) Carbonet was found to be less adherent to discharging wounds. (2) It made the surrounding skin less soggy and allowed the wound to dry more quickly. (3) In one case in which an allergic rash had been caused by paraffin gauze, it caused no reaction and the rash quickly disappeared. From these results, I have come to the conclusion that Carbonet is a superior dressing to paraffin gauze. Incidentally, I found it a very suitable dressing when applied over an antibiotic ointment on an infected wound'.

The second report comes from St. George's Hospital, London, S.W. 1: 'The Carbonet was applied as an initial basic dressing to ordinary surgical wounds in 27 patients. These were predominantly abdominal wounds but included radical mastectomy and thyroid cases as well. The technique was to apply the Carbonet, cover this with a thick layer of ordinary gauze and then keep the dressing in place with porous Elastoplast. In no case did sepsis occur, and the wounds on first dressings were never greasy or soggy. On removal, the dressings did not adhere to the wound, and there appeared to be no pain caused by catching of the mesh in the sutures. In my opinion, Carbonet is the best non-adherent dressing I have tested for routine surgical wounds'.

Carbonet is available in tins containing 36 sterile dressings measuring $3\frac{3}{4} \times 3\frac{3}{4}$ inches, and in tins containing a continuous, sterile strip of material $7\frac{1}{2}$ inches wide and 4 yards long. Further information can be obtained from Smith & Nephew (Pty.) Ltd., P.O. Box 92, Pinetown, Natal.

FUNGIZONE FOR INFUSION

Squibb Laboratories (Pty.) Ltd. introduce a new Squibb product 'Fungizone (Amphotericin B) for Infusion, and supply the following information:

Fungizone is a potent antibiotic. The physician planning to use this drug should be fully acquainted with its properties.

Fungizone (Amphotericin B) is a new antifungal antibiotic. For intravenous use, it is supplied as a sterile lyophilized powder in vials providing 50 mg. of amphotericin B and a total of approximately 46 mg. of sodium desoxycholate with sodium phosphates as a buffer. For administration by intravenous infusion, the dry Fungizone powder should be dissolved in Dextrose Injection 5% U.S.P.

Amphotericin B is derived from an unidentified *Streptomyces* species found in a South American soil sample. The isolation, crystallization and biochemical characterization of the antibiotic was achieved in the laboratories of the Squibb Institute for Medical Research. Since crystalline Amphotericin B is practically insoluble in aqueous media, an amphotericin-B sodium desoxycholate mixture was developed, resulting in a solubilized material. Clinical evidence indicates that Fungizone is effective against a wider variety of deep-seated fungi and yeasts than any other antifungal agent now available for use in man. The antibiotic is without effect on bacteria. Demonstrable blood levels of the antibiotic persists for 18 hours after intravenous infusion is discontinued, suggesting that the antibiotic is slowly excreted by the kidneys.

Storage. Vials of dry Fungizone powder should be stored in the refrigerator, protected against exposure to light. Freshly prepared solutions may be stored at room temperature for 24 hours with a minimum loss in potency; solutions must be protected against exposure to light, and any unused material should be discarded after 24 hours.

Indications. Fungizone for infusion is specifically intended for the treatment of disseminated mycotic infections, including coccidioidomycosis, cryptococcocis (torulosis), disseminated moniliasis, histoplasmosis, and North American blastomycosis.

Administration. Fungizone should be administered by *slow* intravenous infusion over a period of approximately 6 hours, observing the usual precautions for intravenous therapy. The recommended concentration for intravenous infusion is 0·1 mg. per c.c. (1 mg. per 10 c.c.). The infusion solution is prepared by adding 10 c.c. of Dextrose Injection 5% U.S.P. to the dry Fungizone powder to provide an initial concentration of 5 mg. per c.c.; shake the vial vigorously until a clear solution is obtained. The recommended concentration of 0·1 mg. per c.c. (1 mg. per 10 c.c.) is then obtained by further dilution with Dextrose Injection U.S.P.

Dosage. Since tolerance to Fungizone varies individually, dosage must be adjusted to the specific requirements of each patient. Therapy should be instituted with a daily dose of 0·25 mg. per kg. of body-weight and *gradually increased* until an optimum level is attained. Generally, total daily dosage may range up to a level of 1·0 mg. per kg. of body-weight. Within this range, dosage should be maintained at the highest possible level that is *not accompanied by toxic manifestations* (headache, nausea, vomiting, or rise in blood urea nitrogen or non-protein nitrogen). In seriously ill patients not benefited by daily doses of 1 mg. per kg. this dose may be exceeded cautiously and gradually up to a maximum daily dose of 1·5 mg. per kg., *provided no toxic effects are encountered.* Since Fungizone is excreted very slowly, therapy may be given on alternate days in patients on the higher dosage schedule. *Caution. Under no circumstances should total daily dosage of 1·5 mg. per kg. be exceeded.* When improvement is observed, daily administration of the antibiotic may be changed to therapy on alternate days. Duration of therapy depends on the nature and severity of the infection. In clinical experience to date, significant improvement has been observed in most instances after 4-8 weeks of treatment. A shorter period of therapy appears to produce a less favourable response and may lead to relapse.

Precautions. Transient anorexia, chills and fever are frequently encountered during the first few days of Fungizone therapy; thereafter, however, these reactions generally diminish and tend to be less troublesome. Administration of antipyretics and/or antihistamines is helpful in minimizing these side-effects. If febrile reactions occur during the infusion, administration of the drug should be interrupted to allow the patient to recover from the episode. Headache, nausea and vomiting are early toxic manifestations of the antibiotic, requiring a reduction in the total daily dosage. Blood urea nitrogen (BUN) and non-protein nitrogen (NPN) levels should be checked as a routine during Fungizone therapy. BUN and NPN levels should not exceed 20 mg.% and 40 mg.% respectively. If increased BUN or NPN levels are observed, Fungizone therapy should be interrupted for 7 days or longer until the level returns to normal limits. When medication is reinstated, therapy should be resumed by starting with the lowest dosage level, i.e. 0·25 mg. per kg. of body weight and increasing gradually to an optimum level as outlined above under *Dosage*.

As with other intravenously administered drugs, local inflammatory reactions at the injection site or thrombophlebitis may occur in some patients. Thrombophlebitis may be minimized by decreasing the concentration of the infusion solution below 0·1 mg. per c.c., reducing the rate of infusion, and using a smaller-guage needle.

Caution: If other toxic manifestations occur during the course of therapy, discontinue Fungizone immediately.

REVIEWS OF BOOKS : BOEKRESENSIES

DIAGNOSIS AND TREATMENT OF INFECTIONS

The Diagnosis and Treatment of Infections. By D. Geraint James, M.A., M.D. (Cantab.), M.R.C.P. (London). Pp. viii + 234. 30s. Oxford: Blackwell Scientific Publications. 1957.

Contents: Preface. *Part 1. Chemotherapeutics.* 1. Chemotherapeutic Agents. 2. Fate in the Body and Mode of Action. 3. Complications of Chemotherapy. *Part 2. Micro-organisms causing human disease.* 4. Fungi. 5. Protozoa and Metazoa. 6. Spirochaetes. 7. Mycobacteria. 8. Gram-positive Bacteria. 9. Gram-negative Bacteria. 10. Rickettsiae. 11. Viruses. *Part 3. Infections of Systems.* 12. Respiratory System. 13. Heart. 14. Central Nervous System. 15. Peritoneum and Intestine. 16. Liver, Biliary Tract and Pancreas. 17. Urinary Tract. 18. Eye. 19. Ear, Nose, Sinuses and Throat. 20. Venereal Diseases. 21. P.U.O. 22. The Use of Corticosteroids in the Management of Infections. Index.

The author, who visited South Africa last year with his wife, Dr. Sheila Sherlock, and rapidly confirmed his growing reputation as a clinician and lecturer, has set himself a very ambitious target in writing this book. He has endeavoured, in the short space of 224 pages, to describe and integrate the clinical and laboratory diagnosis of diseases caused by micro-organisms with their treatment by chemotherapy. The result is a masterpiece of compression, with some of the attendant faults and disadvantages thereof.

The style is didactic, succinct and terse—at times almost telegraphic. The subject matter is factual, up to date and authoritative, but somehow the overall effect is a little disappointing.

The opening (and best) section of the book deals with chemotherapeutic agents in the magement of disease. It is very well written and contains much of value.

The middle section on bacteriology, virology and protozoology is conventional and adequate, but the final section, which comprises descriptions of the infections as they affect the various systems, does not attain the standard of the earlier portions. The author has done some drastic pruning here, and many of the resultant clinical sketches of diseases read like the potted biographies of 'Who's Who' or Debrett's Peerage.

There is, unavoidably, a certain amount of repetition between the various sections of the book, which also contains 24 well devised, informative tables and a good index.

It is manifestly impossible to write a completely satisfactory book of manageable proportions on this vast theme. Nevertheless, Dr. James has made a commendable and courageous attempt to do so. The viewpoint throughout is largely clinical, and the therapeutic advice offered is sound and very well balanced.

The book was especially designed for senior medical students, interns and registrars. It could also be read with profit by many general practitioners and consultants.

J.S.

AIDS TO BACTERIOLOGY

Aids to Bacteriology. Ninth Edition. By H. W. Scott-Wilson, B.Sc., B.M., B.Ch. (Oxon). Pp. vii + 403. 12s. 6d. London: Baillière Tindall and Cox Ltd. 1957.

Contents: The General Biology of Bacteria. II. Infection and Immunity. III. Nomenclature and Classification. IV. Bacteriological Apparatus. V. The Preparation and Use of Nutrient Media. VI. The Microscopic Examination and Staining of Bacteria. VII. Micro-Organisms of Acute Inflammation and Suppuration. VIII. Neisseria. IX. Haemophilus, Moraxella and Brucella. X. The Diphtheria Bacillus and Allied Organisms. XI. The Acid-Fast Bacilli. XII. The Coli-Aerogenes Group. Proteus and Pneumobacillus. XIII. Salmonella and Shigella. XIV. The Vibrios. XV. Pasteurella and Malleomyces. XVI. Spore-Forming Organisms. XVII. Miscellaneous Bacteria of Medical Importance. XVIII. Actinomyces, Actinobacillus and Nocardia. XIX. The Spirochaetes. XX. Rickettsia. XXI. Viruses and Virus Diseases. XXII. The Pathogenic Fungi. XXIII. The Pathogenic Protozoa. XXIV. Chemotherapy of Bacterial Diseases. XXV. The Bacteriology of Sewage, Soil and Air. XXVI. The Bacteriology of Water. XXVII. The Bacteriology of Foodstuffs and Milk. XXVIII. Sterilization and Disinfection. Appendix. Index.

This well-known member of the 'Aids' series has now reached its ninth edition. Although the scope and general arrangement of the book is similar to the previous edition, it has been revised and brought up to date. The latest matter has been included without adding much to its size by the condensation of some of the less important material.

A new addition is an Appendix in which bacteria are grouped according to their outstanding characteristics, thus making for easier identification of organisms.

The value of the 'Aids' series to medical students is well known and there must be few who have not made use of them at some time.

A.H.T.

IMMUNOPATHOLOGY

Immunopathologie in Klinik und Forschung und das Problem der Autoantikörper. Herausgegeben von P. Miescher und K.O. Vorlaender. XVI + 598 Seiten. 119 Abbildungen, in 171 Einzeldarstellungen. DM. 69.—. Stuttgart: Georg Thieme Verlag. 1957.

Contents: Experimentelle Grundlagen. I. Grundbegriffe der Immunologie. II. Antierythrocytäre Antikörper. III. Die experimentellen Grundlagen der Immunologie der Leukocyten und Thrombocyten. IV. Gegen Niere gerichtete Antikörper. V. Gegen Leber gerichtete Antikörper. VI. Die immunologischen Grundlagen rheumatischer Gewebsreaktionen. VII. Die experimentellen Grundlagen der Encephalomyelitis. *Klinik.* I. Die erworbenen hämolytischen Anämien. II. Die Immunohämatologie der Leukocyten und Thrombocyten. III. Immunologisch bedingte vaskuläre Purpuraformen. IV. Immunoplasmopathien. V. Immunologische Vorgänge bei Nierenerkrankungen. VI. Immunologische Vorgänge bei Lebererkrankungen. VII. Immunologische Vorgänge bei rheumatischen Erkrankungen. VIII. Immunologische Vorgänge bei Schilddrüsenerkrankungen. IX. Der viscerale Erythematodes. X. Immunologische Vorgänge bei der Polyneuritis und bei Entmarkungskrankheiten. XI. Organ-Homotransplantation. Experimentelle Grundlagen und klinische Verwendung. XII. Sympathische Ophthalmie und Endophthalmitis phacoanaphylactica. Namenverzeichnis. Sachverzeichnis.

The authors give a very interesting introductory chapter on antigens and antibodies with special reference to globulin fractions as determined by electrophoretic means.

They also discovered that the speed of electrophoretic migration of the globulins depends on the size of the molecules and the way in which the antibodies combine with the toxins. The role played by lymphocytes and histiocytes is discussed, with special reference to increased antibody titre. The authors are of the opinion that most, if not all antibodies, originate in plasmacells although lymphocytes cannot confidently be excluded. They also hold the view that plasmacells precede the lymphocyte stage. It is also pointed out that the newborn belonging to animals with multi-core placentas, get their antibodies from colostrum—unlike human beings.

Haptenes and their antigenicity are discussed in relation to substances like Dextran and lipo-polysaccharides. All antibodies are said to be proteins and its formation is therefor bound up with structures involving amino-acids, hormones, CNS, and other proteins. Special mention is made of ribonucleic acid.

The theories of Burnet and Fenner are discussed with reference to the belief that enzymes and daughter cells are a prerequisite to antibody formation. This in turn also explains antibody-specificity. Under this heading phenomena inclusive of Arthus phenomenon, allergy, asthma, urticaria and anaphylaxis are appropriately taken into review. Erythrocytes and heterophile antibodies are discussed with special emphasis on Forsman-antigens.

The section on antigen-antibody reaction in kidney disease is very interesting. The antigen-antibody reaction is discussed with special emphasis on chemical structure and the importance of desoxypento-nucleic acid. Radio-active iodine was used as the antibody tracer and the value of streptolysin as a code to streptococcal activity pointed out.

Antibody reaction to liver extracts is described and the regeneration with complications enumerated. The chapter on anti-erythrocyte antibodies is very good and very well illustrated. Cold and warm agglutinins with the technique of tracing are described. Fuadin and chinidin are mentioned as possible causes of anti-erythrocyte immunising antibodies with subsequent anemia.

Phagocytosis of such erythrocytes is discussed. Interesting also is the fact that auto-antibodies could be demonstrated against polmorphs, lymphocytes, monocytes and nuclear rests. No antibodies could be demonstrated against eosinophils or basophils. All of the α-globulin type.

D.J.H.

YEAR BOOK OF MEDICINE

The Year Book of Medicine (1957-1958 *Year Book Series*). Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D. and Philip K. Bondy, M.D. Pp. 752. 128 Figures. $7.50. Chicago: Year Book Publishers, Inc. 1957.

Contents: Part I. Infections. Antimicrobial Therapy. Steroid Therapy in Infection. Staphylococcic Infections Acquired in Hospitals. Staphylococcic Infections, General. Salmonella Infections. Bacterial Endocarditis. Urinary Infections Acquired in Hospitals. Leptospirosis. Tetanus. Tuberculosis. Fungous Infections. New Knowledge of Viral Diseases. Poliomyelitis. Varicella. Variola. Psittacosis. Herpes Zoster. Infectious Mononucleosis. Protozoan and Metazoan Infections. Rheumatoid Arthritis. Collagen Diseases. Diseases of Unknown Etiology. Fever. Bacteremia. Host Factors in Infections. *Part II. The Chest.* Pathology. Physiology. Emphysema. Congenital Disorders. Asthma, Bronchitis and Bronchiectasis. Pneumoconiosis and Other Inhalation Diseases. Sarcoidosis. Adenovirus Respiratory Infections. Friedlander's Pneumonia, Acute and Chronic. Pulmonary Mycoses. Tuberculosis. Lung Cancer. Miscellaneous. *Part III. The Blood and Blood-forming Organs.* General Topics and Basic Considerations. Hemolytic Anemias. Pernicious and Other Nutritional Macrocytic Anemias. Hypochromic Anemias. Other Anemias. Polycythemias. Spleen and Blood Disorders. Leukocytosis and Leukopenia. Leukemias and Related Disorders. Thrombocytopenic and Vascular Purpuras. Coagulation Defects. Drug-Associated Blood Dyscrasias. *Part IV. The Heart and Blood Vessels and the Kidney.* Congenital Heart Disease. Rheumatic Heart Disease. Atherosclerosis and Coronary Disease. Hypertension. Pathologic Physiology. Electrocardiography and Arrhythmias. Miscellaneous. Disorders of the Pulmonary Circulation. Cerebral Vascular Disorders. Peripheral Vascular Disease. The Kidney. *Part V. The Digestive System.* Alimentary Tract. Liver and Gallbladder. Pancreas. *Part VI. Metabolism.* The Adrenal Glands. The Thyroid Gland. Carbohydrate Metabolism. Calcium, Phosphorus and the Parathyroid Gland. The Pituitary Gland. Lipids and Nutrition. Metabolic Disease. Miscellaneous.

The volume of medical writing continues to increase at an alarming rate. No man born of woman can possibly keep up with the torrent that flows from the presses. Any attempt to do so can only result in utter confusion and frustration. The Year Book series has given considerable relief to many and the 1957-58 Year Book of Medicine has made its welcome appearance. It covers a great deal of the important work in the period May, 1956-1957, and includes infections, diseases of the chest, blood and blood forming organs, heart blood vessels and kidney, the digestive gland and last but not least, metabolism. Such a compilation cannot be reviewed in detail. On the whole the choice of subjects is well balanced and the articles are satisfactorily abstracted. The illustrations are well reproduced. The editorial comments are generally pertinent and valuable. For example (p. 654), like the Editor, the reviewer is sceptical as to the existence of a state of 'metabolic insufficiency'.

Some of the comments are controversial and arresting and deserve to be in heavy and not small print, as on p. 676. 'The catheter is a dangerous instrument which should be used with the respect it deserves. In the long run it seems likely that more people die each year as a remote result of catheterization than from such major procedures as thoracotomies or craniotomies.'

The Year Book is a valuable aid to both physician and practitioner in keeping abreast with many of the facets of Internal Medicine.

E.L.

THE LYMPHATIC SYSTEM

Lymphatics, Lymph and Lymphoid Tissue. By Joseph Mendel Yoffey, D.Sc., M.D. (Manch.), F.R.C.S. (Eng.) and Frederick Colin Courtice, M.A., D.Phil. (Oxon.), D.Sc. (Sydney), F.R.A.C.S. (Hon.). Pp. vii + 510. 99 Figures. 60s. net. London: Edward Arnold (Publishers) Ltd. 1956.

Contents: 1. General Arrangement and Organization of the Lymphatic System. 2. The Formation of Lymph. 3. Physiological Significance of Regional Lymphatics. 4. Lymph Flow, Lymph Pressure and Lymph Composition. 5. Biological Significance of Lymphoid Tissue. 6. Cell Content of Lymph. 7. The Lymphocyte. 8. Practical Considerations. Author Index. Subject Index.

The second edition of this book is some 20% larger than the first, and one of the authors' main difficulties has been one of compression, in view of the abundant literature since 1940. The approach is physiological, and much of the work discussed is necessarily based on laboratory animals.

The morphological description of the lymphatic vessels is factual and relatively free from debateable matters, but it does reveal surprising gaps in our knowledge in the human. The next three chapters, taking up about half the volume, give a clear and up-to-date summary of our knowledge on the formation and significance of lymph and lymphoid tissue, and will prove of great interest and value to a wide range of medical readers.

The next two chapters on the cell content of lymph and on the lymphocyte give the impression that very little is known or generally accepted of the functions and potentialities of the lymphocyte. Part of this seems to be the result of some of the quoted authors accepting a wide morphological range for what they regard as lymphocytes, and some results from the basic difficulty of separating functionally the two components of lymph nodes, the lymphocyte and the reticulo-endothelial cell. But some at least is due to the historical approach to each section, where the older reviews seem to get as much space and prominence as the more recent opinions, based on data obtained by means unavailable to the earlier writers. The final chapter on practical considerations refers to many important matters such as hunger oedema, ascites and the lymphatic spread of tumours, but from lack of space some of these are discussed very briefly.

The authors have done a great service in putting together the many opinions and facts on this important subject, which today forms one of the many bridges between physiology and modern medicine.

T.J.

PRACTICAL ZOOLOGY

Practical Biology for Advanced Level, Medical and Intermediate Students. Volume I: Practical Zoology. 4th Edition. By C. J. Wallis, M.A. (Cantab.) Pp. x + 317. 175 Figures. 24s. net. London: William Heinemann—Medical Books—Ltd. 1957.

Contents: Foreword to the Fourth Edition. Preface. Introduction. *Part I. Microscopical Technique. Part II. Animal Biology.* Section I. Animal Morphology and Anatomy. Section II. Animal Cytology and Histology. Section III. Animal Physiology. Section IV. Vertebrate Embryology. *Appendices.* I. The Preparation of Reagents. II. Biological Methods. III. Equivalents, Conversion Table. IV. Treatment of Accidents in the Laboratory. V. Firms Supplying Biological Apparatus and Material. Index.

This textbook is designed to meet the practical requirements of a number of examination syllabi including those for the English General Certificate of Education and for the London Conjoint Board. In its fourth edition the book appears in two volumes, volume I being devoted to zoology.

There is undue emphasis on details of morphology, inevitable in a book of this nature, and some of the biochemical tests described have been superseded in most laboratories but apart from this the book is up to date in its approach. As an elementary textbook it is remarkably comprehensive but the species selected as examples are mostly those readily available in England. The South African student would need to be on his guard to detect morphological differences between his local species and those described in the text.

The style is clear and concise and the diagrams adequate. The practical instructions are sensible and cover a wide range of procedures. A useful appendix, for those who do not wish to limit their practical teaching to locally available species, is a list of firms which supply biological material.

A.S.

CORRESPONDENCE : BRIEWERUBRIEK

LICENSING OF X-RAY MACHINES

To the Editor: I have read with interest Dr. M. Weinbren's note and your footnote in the issue of 29 March 1958.

In a purely personal capacity I should like to associate myself with his plea for licensing all X-ray machines in this country.

L. J. A. Loewenthal

604 Medical Centre
209 Jeppe Street
Johannesburg
2 April 1958

COMBINED INVESTIGATIONS

To the Editor: At the last National Meeting of the Southern African Cardiac Society, it was agreed upon a proposal by Dr. Len Braudo to encourage combined investigations by various centres in this country. It was felt that these combined efforts would be able to cover a large amount of material and thus be of value. It is hoped that the communications in this issue by Dr. V. Schrire of Cape Town and Drs. B. A. Bradlow and M. M. Zion of Johannesburg, presented under the aegis of the Southern African Cardiac Society, will be the first of many such examples of cooperative endeavour.

Maurice Nellen
National Chairman, S.A. Cardiac Society

903 Medical Centre
Heerengracht
Cape Town
25 March 1958

'AEROSPORIN' (POLYMYXIN B SULPHATE)

To the Editor: We should like to refer to the editorial[1] of 14 December 1957, in which it is stated that polymyxin is too toxic for systemic use. This statement appears to be based on the original work on the nephro-toxicity of polymyxin A, the first polymyxin to be described.

The polymyxin at present available is polymyxin B sulphate ('Aerosporin') which has now been in use for over 8 years, and has been shown both experimentally and clinically to be comparatively safe when administered systemically in therapeutic dosage. (Moyer, J. H., Mills, L. C. and Yow, E. M. (1953): Arch. Intern. Med., **92**, 238. Swift, P. N. and Bushby, S. R. M. (1953): Lancet, **1**, 110. Yow, E. M. and Moyer, J. H. (1953): Clin. Res. Proc., **1**, 47. Yow, E. M. and Moyer, J. H. (1953): Arch. Intern. Med., **92**, 248).

In view of the great value of 'Aerosporin' in infections which do not respond to other antibiotics and where it may be life-saving, we feel that its suitability for systemic administration should be more widely known.

A booklet on 'Aerosporin' and its uses is obtainable from Burroughs Wellcome & Co. (S.A.) Ltd., P.O. Box 10293, Johannesburg.

J. M. Frisch
Medical Information Department

Burroughs Wellcome & Co.
Euston Road
London, N.W. 1
1 April 1958

1. Editorial (1957): S. Afr. Med. J., 31, 1265.